FDA Antiviral Drugs Advisory Committee Meeting

Boceprevir Capsules

(NDA 202-258)

29-March-2011

Briefing Document

Available for Public Disclosure

Without Redaction

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2.0 SUMMARY

Chronic hepatitis C (CHC) affects approximately 170 million people worldwide and 3.2 million in the United States. CHC is a leading cause of liver disease, including liver failure and hepatocellular carcinoma. In the U.S., infection with hepatitis C virus (HCV) genotype 1 is the most common and is also the least responsive genotype to approved therapies. Currently, the recommended treatment for CHC genotype 1 infection is a 48-week course of peginterferon combined with ribavirin. Sustained virologic response (SVR) to treatment, as defined by the absence of detectable hepatitis C virus 24 weeks after the end of treatment is achieved in only ~40% of patients. In addition, treatment is often poorly tolerated because of side effects that may prevent patients from completing a 48-week course of therapy.

Boceprevir is a member of the class of ketoamide protease inhibitors that inhibit viral replication by binding to the active site of the HCV non-structural protein 3 (NS3) protease; other members of this class include telaprevir. Boceprevir has demonstrated potent in vitro antiviral activity against HCV genotypes 1a and 1b. Boceprevir is primarily metabolized via aldoketoreductase (AKR) with less extensive CYP3A4 metabolism. Drug-drug interactions are predictable and manageable. No dose adjustment of boceprevir is required in patients with hepatic or renal impairment. A thorough QT study showed that boceprevir had no clinically relevant effects on the QT interval. Phase 1 studies of boceprevir demonstrated a favorable pharmacokinetic (PK), metabolic and safety profile. The results of Phase 2 studies confirmed the antiviral activity of boceprevir against HCV activity, and supported the evaluation of boceprevir at a dose of 800 mg three times daily (TID) in Phase 3.

In two large, double-blind Phase 3 clinical studies conducted in treatment-naïve patients (SPRINT-2; P05216) and patients who had previously failed treatment with peginterferon and ribavirin (RESPOND-2; P05101), boceprevir given with peginterferon alfa-2b and ribavirin produced significantly higher SVR rates compared with a standard 48-week course of peginterferon alfa-2b and ribavirin (SVR is ~1.7 times higher among treatment-naïve patients and ~2.8 times higher among patients who had previously failed treatment). Consistently higher response rates were observed across baseline sub-groups, including populations who are usually poor responders, such as blacks and previous treatment non-responders, demonstrating that the addition of boceprevir to peginterferon and ribavirin represents a significant improvement over the current standard of care. In addition, a Phase 3 study (P05685) of boceprevir given with peginterferon alfa-2a and ribavirin has confirmed the safety and efficacy of boceprevir when administered with peginterferon alfa-2a. Data being collected in a long term follow-up study (P05063) support the conclusion that virologic responses obtained with boceprevir are durable.

The boceprevir pivotal Phase 3 clinical program evaluated a novel response-guided therapy (RGT strategy which individualized treatment duration based on early HCV RNA response. Approximately one-half of patients in boceprevir RGT arms received a shorter duration of therapy, and SVR rates were superior to 48-weeks of peginterferon and ribavirin. The Phase 3 program also featured a unique concept of

initiating therapy with peginterferon and ribavirin for the first four weeks – the lead-in period – prior to adding boceprevir. The potential value of the lead-in is to (1) lower HCV RNA levels and optimize ribavirin and interferon activity prior to exposure to boceprevir thereby reducing the risk of resistance development, and (2) test peginterferon and ribavirin compliance and tolerability prior to adding boceprevir. The lead-in paradigm also enabled an on-treatment, real-time assessment of early interferon responsiveness, an important prognostic factor for subsequent SVR.

The emergence of viral resistance was evaluated in the boceprevir clinical development program. Viruses with decreased susceptibility to boceprevir (resistance-associated variants, RAVs) were detected in 7% of patients prior to treatment in the pivotal Phase 3 studies. There was no association noted between the detection of *baseline* RAVs and subsequent response to treatment. In contrast, in most instances, patients experiencing viral breakthrough during boceprevir therapy had RAVs detected. Data from the long-term follow-up study (P05063) demonstrate that RAVs diminish over time.

The safety profile of boceprevir has been characterized in more than 2000 boceprevir-treated patients, including over 1500 patients who received boceprevir at the proposed clinical dose of 800 mg three times daily (TID) in combination with peginterferon alfa-2b and ribavirin in the pivotal Phase 3 studies (SPRINT-2 and RESPOND-2) and in the Phase 2 treatment-naïve study (SPRINT-1; P03523). The addition of boceprevir for up to 44-weeks was generally well tolerated, and side effects were primarily those previously described in patients treated with peginterferon and ribavirin alone. The most common adverse events observed were flu-like symptoms that are typically reported with peginterferon and ribavirin therapy.

Anemia (and to a lesser extent, neutropenia) was reported more frequently in boceprevir-containing treatment arms compared with control. Anemia was managed with the use of erythropoietin and/or ribavirin dose reduction; discontinuation of therapy due to anemia was infrequent. Dysgeusia, a change in the sense of taste, was more common with boceprevir therapy, but was not severe or treatment-limiting. Overall, rash was reported with a similar incidence in boceprevir-containing treatment arms compared with control. There was no evidence to suggest that the rash reported with boceprevir differed in character or severity from that described in conjunction with ribavirin. There were no reported cases of Stevens-Johnson syndrome/toxic epidermal necrolysis.

This briefing document provides an overview of the development of boceprevir, including preclinical and clinical data which support the conclusion that boceprevir 800 mg TID in combination with peginterferon alpha and ribavirin:

- Fulfills a significant unmet medical need for the treatment of chronic hepatitis C genotype 1 infection.
- Produces a clinically and statistically significant increase in SVR rates over standard of care.

- Offers an individualized approach to therapy by using on-treatment response to determine treatment duration, allowing early responders to achieve robust SVR rates with short treatment duration.
- Is efficacious in a diverse group of patients, including the most difficult to treat populations (e.g., blacks and patients with poor interferon responsiveness).
- Has a favorable benefit/risk profile.

The proposed prescribing indication is:

- Boceprevir is indicated for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alpha and ribavirin, in adult patients (18 years and older) with compensated liver disease who are previously untreated or who have failed previous therapy.

A unique dosage and administration is proposed based on the response-guided therapy algorithm implemented in the pivotal Phase 3 studies which allowed many patients to receive a shorter duration of therapy.

Given boceprevir's potential to address a serious unmet medical need, the FDA has granted the boceprevir application a priority review.

3.0 BACKGROUND

CHC poses a major challenge, not only to individuals who are infected, but to health care providers and health care systems. The World Health Organization (WHO) estimates that approximately 170 million people, 3% of the world's population are infected with hepatitis C; and that 3-4 million new infections occur each year.[1,2] Hepatitis C virus (HCV) infection is a major cause of chronic liver disease worldwide, and the leading cause of liver transplantation in developed countries.

It is estimated that approximately 3.2 million Americans are chronically infected with hepatitis C. In the National Health and Nutrition Examination Survey (1999–2002), persons aged 40- to 49-years accounted for 66% of the HCV-infected population and the prevalence of HCV infection among 40- to 49-year-olds was 2.7 times higher than the overall prevalence in the United States.[3]

The standard of treatment of CHC is combination therapy with peginterferon alpha and ribavirin. Achieving SVR has been associated with a significantly reduced risk of liver-related mortality and all cause mortality. The long-term clinical benefit of successful treatment has been shown to extend to patient populations with substantial comorbidities (e.g., cirrhosis, coronary artery disease, hypertension and diabetes).[4] Of the six major HCV genotypes, infection with genotype 1 is most common in the United States (70 to 90%) and is also the least responsive to treatment with SVR rates of less than 50%.[5] Response rates are even lower among blacks and patients with cirrhosis. Among HCV genotype 1 patients who fail a

standard 48-week course of peginterferon and ribavirin therapy, re-treatment leads to SVR in only about 10% of cases.

Under diagnosis, under treatment, and lack of effective therapies can lead to long term complications from the disease. In the U.S., CHC with end-stage liver disease and cirrhosis is currently the leading reason for liver transplantation, accounting for 40% of all liver transplants.[6] While liver transplantation can be life-saving, it is not a cure for hepatitis and recurrent HCV post-transplant is typically a more aggressive disease. Approximately 10%-12% of potential recipients die before they can receive a transplant because of a shortage of donor livers.[6] Hepatocellular carcinoma (HCC) is another important long term complication of HCV infection. The WHO estimates that HCV accounts for 50-76% of all HCC cases worldwide.[7] The incidence of HCV-related HCC in the United States has been increasing and is projected to peak in 2019 at 14,000 cases.[8] In 2004, there were 419,000 hospitalizations and 2,747,000 ambulatory care visits due to HCV infection.[9] Currently, HCV contributes to 12,000 deaths annually.[10] The CDC and other published models predict that the incidence of HCV-related sequelae will rise in the coming decades. This rise in HCV-related liver disease over the next 10–20 years will significantly affect the health system.[11]

There is a clear need for new therapies that are more effective than current options, and have the potential to increase SVR rates and reduce the future burden of HCV and its complications.

4.0 MICROBIOLOGY

4.1 Mechanism of Action

Boceprevir is a novel peptidomimetic HCV NS3 protease inhibitor. The mechanism of inhibition involves formation of a stable, reversible covalent bond between the ketoamide of boceprevir and the active site serine of NS3 protease. NS3 is an essential virally-encoded enzyme that cleaves the HCV polyprotein at specific sites to form the functional proteins required for viral replication. Like other protease inhibitors, boceprevir is given with peginterferon and ribavirin to minimize the emergence of viral resistance.

4.2 Antiviral Activity *in vitro*

Boceprevir demonstrated activity against HCV genotypes 1a and 1b proteases when evaluated in a biochemical assay for slow binding inhibitors of the NS3 protease. Boceprevir inhibited single chain NS3 with an inhibition constant of approximately 14 nM for genotypes 1a and 1b.

Boceprevir has shown potent antiviral activity in the hepatitis C virus replicon system. These studies were conducted using a replicon system that expresses HCV non-structural genes NS3-NS5B and allows for autonomous replication of HCV sub-genomic RNA; the genotype 1a and 1b replicons were derived from the H77-S and Con1 HCV isolates, respectively. Boceprevir suppressed HCV replicon synthesis following 72 hour exposure, with IC_{50} and IC_{90} values of 200 nM and 400 nM,

respectively. Loss of replicon RNA appears to be first-order with respect to time of treatment. Treatment at the IC_{90} for 72 hours resulted in a 1 log_{10} drop in replicon RNA. Prolonged exposure resulted in a 2 log_{10} decrease in RNA levels by Day 15.

Boceprevir showed additive antiviral activity when administered in combination with interferon alpha in the HCV replicon assay.

4.3 Resistance *in vitro*

The potential for HCV to develop boceprevir resistance was evaluated in *in vitro* resistance selection experiments using an HCV replicon cell-line and serial passage in boceprevir, and another ketoamide protease inhibitor structurally related to boceprevir. Putative boceprevir RAVs in the NS3 protease domain (aa1-181), including the NS3/4a protease cleavage junctions, were identified by clonal sequencing. In addition, an initial analysis of population sequence data from HCV samples obtained from patients enrolled in the Phase 2 study (RESPOND-1) identified additional potential RAVs. Variants at a total of 10 amino acid positions in the HCV NS3 protease domain were identified: V36M/A/L/I/G, Q41R, F43C/S, T54A/C/G/S, V55A/I, R155K/I/M/G/T/Q, A156S/T/V V158M/I, V170A/T/L, and M175L.

To evaluate whether these variants confer phenotypic resistance to boceprevir, they were further characterized in HCV genotype 1a and 1b enzymatic and/or cell-based HCV protease assays (replicon and secreted alkaline phosphatase assays). Boceprevir potency was reduced (2- to-10 fold) by the following RAVs: V36M, T54A, R155K, and V170A. A loss of potency (>50 fold) was observed with the RAV A156T. Replicons carrying the A156T variants were less fit than replicons carrying other RAVs. The fold increase in resistance for NS3 proteases harbouring two or more RAVS was approximately equal to the product of fold resistances for the individual RAVs.

5.0 TOXICOLOGY

Boceprevir was not mutagenic or genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, human peripheral blood lymphocyte and mouse micronucleus assays and not carcinogenic in 2-year rat and mouse carcinogenicity studies.

Boceprevir has been evaluated in acute rat studies and in acute rising dose studies in dogs and monkeys; repeated-dose studies in mice up to three months, in rats up to six months, in monkeys up to twelve months in duration, and in reproductive toxicology studies. No clinically relevant effects were observed in cardiovascular, respiratory, central nervous, gastrointestinal and/or renal systems or on hematologic parameters at the highest doses tested in either dogs or rats. No clinically relevant effects were observed in vitro in isolated dog cardiac purkinje fibers or in the human ether-a-go-go-related gene (hERG) assay. Targets identified in nonclinical studies

consist of the gall bladder, liver, coagulation parameters, and reproductive tract; and were primarily observed in rodents.

Grossly discolored gall bladder was observed in the 2-year mouse carcinogenicity study. The finding had no histopathologic correlate, no inflammation, no evidence of concretions, no long-term impact to gall bladder integrity and no test article-related gall bladder tumors. This finding was not observed in a 3-month study in mice and was not observed in monkeys.

Focal neutrophilic infiltrates in the liver occasionally associated with necrotic hepatocytes were observed in mice after 3 months of dosing. Minimal to mild increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were observed, but there was no direct correlation between neutrophilic liver infiltrates and increased liver enzymes in affected animals. Neutrophilic infiltrates in the liver appear to be species-specific to mice. Multinucleated hepatocytes were identified in the livers of male rats dosed for 3 and 6 months. Minimal to mild increases in ALT/AST levels were also observed in rats, but there was no direct correlation between elevated liver enzymes and multinucleated hepatocytes in affected animals. The finding appears to be gender- and species-specific to male rats.

In a 2-year carcinogenicity study in mice, the incidence of hepatocellular adenomas was increased in female mice at systemic exposures 5.7-fold higher than those in humans at the recommended 800 mg three times daily (TID) clinical dose; there was no increase in incidence at the next highest dose which corresponded to systemic exposure greater than the human exposure at 800 mg TID. There were no increases in mortality or malignancy associated with the hepatocellular adenomas. Although not an inducer of cytochrome p450 (CYP) enzymes in humans, induction of CYP enzymes has been demonstrated previously in mice administered boceprevir, and liver tumors are a recognized sequelae with chronic exposure to an enzyme inducer. There were no increases in the incidence of tumors in male mice at any dose in the study. In rats, no adenomas or carcinomas occurred at any dose.

Single cell hepatocyte necrosis was observed in the 2-year mouse carcinogenicity study. This finding was not observed in the rat or monkey and is likely species-specific to mice. Minimal-to-moderate pigment accumulation in the liver was also observed in the 2-year mouse carcinogenicity study. The pigment stained negative for bilirubin, weakly positive for iron, and positive for lipofuscin. Lipofuscin is considered an “aging pigment” resulting from the catabolism of damaged cells (including red blood cells). A marketed HIV protease inhibitor (atazanavir) appears to have similar findings in mice suggesting that single cell necrosis, chronically, may lead to pigment accumulation.

Increases in aPTT have been observed in monkeys in the absence of clinical or pathology findings that would indicate a defect in hemostasis. Convincing increases in aPTT were only observed with optical detection methods or at very high doses, and there was considerable variability of magnitude and sensitivity of the effect

depending on the dose, instrument or reagent manufacturer. Monitoring of aPTT in clinical studies has revealed no evidence that this finding is clinically relevant in humans.

In rats, boceprevir induced reversible effects on fertility and early embryonic development in female rats with a no effect level (NEL) of 75 mg/kg. At this dose, the rat-to-human exposure multiple is 1.3-fold higher than the systemic human exposure at the 800 mg TID clinical dose. (Therapy is to be contraindicated in pregnant females because boceprevir must be administered with ribavirin [a teratogen] and peginterferon [an abortifacient].)

Decreased fertility was also observed in male rats, most likely as a consequence of testicular degeneration (NEL of 15 mg/kg which represents a rat-to-human exposure multiple of less than 1-fold the human exposure at the clinical dose of 800 mg TID). A trend toward functional recovery in the testes was observed during a 2-month post-dose interval following 3-months of boceprevir administration at a level higher than the clinical exposure. In repeat dose studies, the sequence and progression of the testicular/epididymal findings suggests the Sertoli cell as the primary target of toxicity. Testicular degeneration has not been observed in mice or monkeys and therefore is considered species-specific to rats. Additionally, clinical monitoring of the surrogate marker inhibin B, as well as semen analysis, has revealed no evidence that this finding is clinically relevant in humans.

Since the findings identified in nonclinical safety pharmacology and toxicology studies tend to occur in only a single species (i.e., species-specific) and/or gender, at exposures that are higher than or similar to the intended clinical therapeutic dose, with no similar changes having been observed in humans, the nonclinical findings provide no evidence of a relevant risk to humans.

6.0 CLINICAL PHARMACOLOGY

6.1 Clinical Pharmacology Program Overview

The clinical pharmacology program for boceprevir consists of 20 Phase 1 studies. These include 13 studies in healthy subjects and two special population studies (in hepatically and renally impaired patients), which evaluated the PK and tolerability of single and multiple doses of boceprevir. Also included are 5 studies in patients with CHC, which characterized the multiple-dose tolerability, PK and pharmacodynamics (PD) of boceprevir.

Safety

In general, boceprevir was safe and well tolerated in the Phase 1 program.

Boceprevir administered as a single agent to healthy subjects was not associated with decreases in hemoglobin. In healthy male subjects dosed with boceprevir 800 mg TID monotherapy for 57 days (P05351), boceprevir did not cause anemia, nor was there any effect of boceprevir on red blood cell (RBC) survival, production, or destruction, or

on markers of anemia. Peginterferon and ribavirin therapy is known to decrease red blood cell counts, primarily as a result of hemolysis secondary to ribavirin combined with bone marrow suppressive effects of interferon. Coadministration of boceprevir with peginterferon in CHC patients for ≥2 weeks in Phase 1 studies resulted in a consistent decrease in mean hemoglobin levels, of approximately 1.8 g/dL to 3.1g/dL. There was no apparent relationship between the boceprevir dose and the decrease in hemoglobin levels. (See Section 10.5.1.1 for summary of anemia in the key Phase 2 and 3 studies.)

Administration of boceprevir as a single agent to healthy subjects was also not associated with decreases in neutrophil counts. Peginterferon and ribavirin therapy is known to decrease neutrophil counts, primarily as a result of the bone marrow suppressive effects of interferon. Coadministration of boceprevir with peginterferon in CHC subjects resulted in a decrease in mean neutrophil counts, of approximately 1.5 to 2.8 x 10^9/L. (See Section 10.5.1.2 for summary of neutropenia in the key Phase 2 and Phase 3 studies.)

No effect of boceprevir was seen on semen counts, motility evaluations, or plasma concentrations of inhibin B in male CHC subjects.

Neither therapeutic (800 mg TID) nor supratherapeutic (1200 mg TID) doses of boceprevir were associated with clinically relevant effects on cardiac conduction in a thorough QT study designed according to International Conference of Harmonisation E14 principles.

6.2 Pharmacokinetic Profile of Boceprevir

The PK profiles of single and multiple doses of boceprevir from 50 to 800 mg and 100 mg up to 1200 mg, respectively, have been evaluated.

Absorption

Boceprevir was absorbed following oral administration with a median T_{max} of 2 hours. Steady state AUC, C_{max} and C_{min} increased in a less than dose-proportional manner and individual exposures overlapped substantially at 800 mg and 1,200 mg, suggesting diminished absorption at higher doses. Accumulation is minimal and pharmacokinetic steady state is achieved after approximately 1 day of three times daily dosing.

In healthy subjects who received 800 mg TID alone, boceprevir mean exposure was characterized by AUC(τ) of 6,147 ng.hr/mL, C_{max} of 1,913 ng/mL, and C_{min} of 90 ng/mL. PK profiles were generally similar between healthy subjects and HCV-infected patients.

Effects of food on absorption

Food enhanced the exposure of boceprevir by up to 60% at 800 mg TID dose when administered with a meal relative to the fasting state. The bioavailability of

boceprevir was similar regardless of meal type (e.g., high-fat vs. low-fat) or whether taken 5 minutes prior to eating, during a meal, or immediately following completion of the meal. Based on these findings, boceprevir was dosed with food in Phase 2 and Phase 3 studies.

Distribution

Boceprevir has a mean apparent volume of distribution (Vd/F) of approximately 772 L at steady state. Boceprevir is not highly bound to human plasma proteins (~75% following a single dose of boceprevir 800 mg).

Metabolism

Boceprevir is administered as an approximately equal mixture of two diastereomers which rapidly interconvert in plasma. The predominant diastereomer is pharmacologically active and the other diastereomer is inactive. Studies *in vitro* indicate that boceprevir primarily undergoes metabolism through the aldoketoreductase (AKR)-mediated pathway to ketone-reduced metabolites that are inactive against HCV. After a single 800-mg oral dose of ^{14}C-boceprevir, the most abundant circulating metabolites were a diastereomeric mixture of ketone-reduced metabolites with a mean exposure approximately 4–fold greater than that of boceprevir. Boceprevir also undergoes, to a lesser extent, oxidative metabolism mediated by CYP3A4/5.

Elimination

Boceprevir is eliminated with a mean plasma half-life of approximately 3.4 hours. Boceprevir has a mean total body clearance (CL/F) of approximately 161 L/hr. Following a single 800 mg oral dose of ^{14}C-boceprevir, approximately 79% and 9% of the dose was excreted in faeces and urine, respectively, with approximately 8% and 3% of the dosed radiocarbon eliminated as boceprevir in faeces and urine. The data indicate that boceprevir is eliminated primarily by the liver.

6.3 Effect of Intrinsic and Extrinsic Factors on Boceprevir Pharmacokinetics

For the purposes of assessing the impact of intrinsic and extrinsic factors, a decrease in boceprevir trough concentration at 8 hours postdose of 50% or greater, or an increase in boceprevir area under the curve (AUC) of 2-fold or greater was considered a clinically meaningful alteration in boceprevir PK. The lower bound of comparability was based on Phase 3 data (using modeling and population PK data), which showed that clinical response is similar for C_{min} greater than approximately 100 ng/mL. The upper bound of comparability was based primarily on no observable relationship of safety with increasing dose/exposure, and specifically no observable correlation of boceprevir exposure with hemoglobin decline in Phase 2 and 3 trials. The following assessment of the effect of intrinsic and extrinsic factors is based on these clinically relevant bounds.

6.3.1 Intrinsic Factors

- No clinically significant differences in pharmacokinetic parameters were observed between patients with end-stage renal disease and healthy subjects; no dosage adjustment is required in patients with any degree of renal impairment.

- No clinically significant differences in pharmacokinetic parameters were found in a study of patients with varying degrees of stable chronic liver impairment (mild, moderate and severe); no dosage adjustment is required in patients with liver impairment.

- No gender, race, or age related pharmacokinetic differences have been observed in adult patients.

6.3.2 Extrinsic Factors

Drug-Drug Interactions: Effect of Coadministered Drugs on Boceprevir

Since the biotransformation and clearance of boceprevir involves two different enzymatic pathways (predominant pathway is via AKR, with less extensive CYP3A4/5 metabolism), boceprevir is less likely to be a victim of significant drug-drug interactions with concomitant medications that affect either of these pathways.

- Coadministration with two different potent AKR inhibitors, diflunisal or ibuprofen, did not increase exposure to boceprevir. This may be a consequence of a lack of saturation of the AKR isoforms which are present in multiple tissues.

- Coadministration of boceprevir with two strong CYP3A4 and P-gp inhibitors, ritonavir and clarithromycin, did not notably change the exposure to boceprevir.

- Coadministration with ketoconazole, a third potent inhibitor of CYP3A4 and P-gp, increased exposure to boceprevir (41% increase in C_{max}, 131% increase in AUC), but not to an extent likely to be clinically relevant. In vitro assessments did not show ketoconazole as an inhibitor of AKR isozymes, which suggests a pathway other than P-gp or CYP3A4 may be affected.

- The CYP3A4 inducer efavirenz decreased exposure to boceprevir (44% decrease in C_{min}, 19% decrease in AUC), but not to an extent likely to be clinically significant.

- Coadministration with tenofovir did not notably change the exposure to boceprevir.

- Coadministration with peginterferon alfa-2b did not notably change the exposure to boceprevir.

- Population pharmacokinetic analysis indicated that ribavirin did not notably change the exposure to boceprevir.

Drug-Drug Interactions: Effect of Boceprevir on Coadministered Drugs

Boceprevir is a strong, reversible inhibitor of CYP3A4 and a moderate inhibitor of P-glycoprotein. Boceprevir does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 *in vitro.* In addition, boceprevir does not induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4/5 *in vitro.* Boceprevir is therefore predictable as a perpetrator of CYP3A4 mediated drug-drug interactions, which are well understood and managed relatively easily.

- Medicines metabolized primarily by CYP3A4 may have increased exposure when administered with boceprevir, which could increase or prolong their therapeutic and adverse effects. Coadministration of boceprevir with the probe drug midazolam increased midazolam exposure (AUC) by 5.3-fold. Boceprevir should not be coadministered with drugs metabolized primarily by CYP3A4 that have a known narrow therapeutic index.

- Coadministration of boceprevir with efavirenz did not notably change the exposure to efavirenz.

- Coadministration of boceprevir with tenofovir did not notably change the exposure to tenofovir.

- Coadministration of boceprevir with drospirenone/ethinyl estradiol increased mean drospirenone C_{max} and AUC by 57% and 99%, respectively. There was no notable change in exposure to ethinyl estradiol.

- Coadministration of boceprevir with peginterferon alfa-2b did not change the exposure to peginterferon alfa-2b.

- Population pharmacokinetic analysis of indicated that boceprevir did not notably change the exposure to ribavirin.

6.4 Boceprevir Dose Selection

Initial dose selection in the clinical development program was based on the in vitro IC90 of 200 ng/mL (~400 nM) in a genotype 1b replicon system as a target for boceprevir mean plasma trough concentration. Analyses of two Phase 1 studies in HCV-infected patients suggested a moderate positive correlation between boceprevir C_{min} and early decrease in HCV RNA (treatment weeks 2 to 5). Subsequent Phase 2 data (RESPOND-1) confirmed that boceprevir 800 TID resulted in higher C_{min} than 400 mg TID, and was more effective in rapidly decreasing HCV RNA levels over 5 weeks than 400 mg TID.

A PK model using intensive Phase 1 PK sampling in combination with sparse Phase 2 PK data demonstrated a less than dose proportional increase in boceprevir

exposure (C_{min}, C_{max}, and AUC) at doses ranging from 100 mg TID to 1200 mg TID. The highly overlapping exposures at doses of 800 mg and 1200 mg suggest that 800 mg TID is on the plateau of the dose/exposure curve and that further dose escalation would not likely yield a substantial increase in exposure.

PK values were determined from sparse sampling data collected in the 2 pivotal Phase 3 studies (boceprevir dose of 800 mg TID). Population PK modeling showed a predicted median Cmin exposure of approximately 212 ng/mL, with a range of 58 ng/mL to 614 ng/mL. PK/PD analysis over this range of exposure values adjusted for other significant covariates that affect viral response showed no significant associations of boceprevir PK with SVR. This suggests that exposure achieved at 800 mg TID is on the plateau of the exposure/response curve and that further dose escalation would not likely yield a substantial increase in efficacy.

The addition of boceprevir to peginterferon and ribavirin has been associated with an incremental decrease in hemoglobin concentration beyond that observed with PR alone (See Sections 6.1 and 10.5.1.1). Therefore, the relationship of PK of boceprevir and anemia was investigated. No observable dose relationship with hemoglobin decline was seen in Phase 1 studies during boceprevir plus peginterferon treatment. In the Phase 2 dose finding study (RESPOND-1), there was no correlation between boceprevir exposure (AUC, Cmax or Cmin) with hemoglobin decline. The Phase 3 PK/PD analysis determined that boceprevir PK parameters were not significantly correlated with incidence of anemia. In contrast, ribavirin PK was significantly correlated.

7.0 OVERVIEW OF BOCEPREVIR CLINICAL DEVELOPMENT

7.1 Overview of the Clinical Development Program

An extensive Phase 2 and Phase 3 clinical development program assessed the efficacy and safety of boceprevir in the treatment of chronic hepatitis C infection (Table 1). A brief overview of the Phase 2 and Phase 3 clinical studies is provided below:

7.1.1 Phase 2 Studies

- Phase 2 dose finding in treatment-failure patients (P03659; RESPOND-1): This early Phase 2 dose finding study was conducted in CHC genotype 1 patients who had never achieved undetectable HCV RNA on peginterferon/ribavirin and had either (1) a prevous treatment duration of 12 weeks and a <2.0 $\log_{10}$ reduction in HCV RNA after 12 weeks of treatment ("null responders") and no dose reductions or interruptions or (2) a previous treatment duration of greater than 12 weeks and received ≥80% of assigned doses and ≥80% of treatment duration. The initial doses of boceprevir investigated in this study were 100 mg, 200 mg, 400 mg TID with peginterferon alfa-2b ± ribavirin; the protocol was amended to add an arm investigating boceprevir 800 mg TID combined with peginterferon (after a 1-week peginterferon lead-in), and later amended to switch patients in all arms of the study

to boceprevir 800 mg TID with peginterferon and ribavirin. None of the patients received boceprevir 800 mg TID in combination with peginterferon and ribavirin from the beginning of the study, and none received more than 24 weeks of boceprevir 800 mg TID with peginterferon and ribavirin.

This study provided evidence that: 1) the addition of boceprevir to peginterferon and ribavirin is generally safe; 2) boceprevir has antiviral activity in patients who previously failed treatment with peginterferon and ribavirin; and 3) ribavirin must be included as part of the boceprevir treatment regimen in order to optimize efficacy. When analyzed retrospectively, the study results supported the use of a 4-week lead-in with peginterferon and ribavirin before the addition of boceprevir and supported the further evaluation of 36 week treatment duration in previous treatment failure patients with an early virologic response.

- Phase 2 study in treatment-naïve patients (P03523; SPRINT-1): This Phase 2 study was conducted in treatment-naive CHC genotype 1 patients and was designed to evaluate the safety and efficacy of boceprevir when added to peginterferon and ribavirin in treatment-naive patients.[12] The study investigated boceprevir at a dosage of 800 mg TID combined with peginterferon and ribavirin for treatment durations of 28 weeks versus 48 weeks, with and without a 4-week lead-in of peginterferon and ribavirin (PR lead-in) before the addition of boceprevir, and also evaluated the efficacy of initiating therapy with low-dose ribavirin.

  The study demonstrated that boceprevir added to peginterferon and ribavirin after a 4-week lead-in had the potential to double the SVR rate compared with standard treatment with peginterferon and ribavirin alone (54% and 56% in the 28-week boceprevir treatment arms with and without PR lead-in, respectively; 75% and 67% in the 48-week boceprevir treatment arm with and without PR lead-in, respectively; and 38% in the 48-week peginterferon and ribavirin control arm). There was a decrease in the rate of viral breakthrough in both the 28- and 48-week boceprevir treatment arms containing the PR lead-in compared to no PR lead-in (4% vs 7% for 28-week arm, and 5% vs 12% for 48-week arm, respectively).

  Data from this Phase 2 study supported: (1) the use of a 4-week PR lead-in prior to the addition of boceprevir; (2) the use of a treatment week 8 assessment of early virologic response to guide treatment duration (response-guided therapy, see Section 7.2.5); and 3) the need for full-dose ribavirin therapy.

7.1.2 Pivotal Phase 3 Studies

- Phase 3 study in treatment-naïve patients (P05216; SPRINT-2): This pivotal Phase 3 study was conducted in CHC genotype 1 patients who were treatment-naive and compared treatment with peginterferon alfa-2b (PegIntron®) and ribavirin for 48 weeks with two treatment regimens containing boceprevir 800 mg TID: response-guided therapy (RGT) and fixed-duration therapy.[13] Peginterferon and ribavirin were administered for the first 4 weeks – the PR lead-in period – prior to

adding boceprevir. The results from this study showed that the addition of boceprevir to peginterferon and ribavirin significantly increased the SVR rate compared with standard treatment with peginterferon and ribavirin alone, and supported the use of early on-treatment response to determine treatment duration.

- Phase 3 study treatment-failure patients (P05101; RESPOND-2): This pivotal Phase 3 study was conducted in CHC genotype 1 patients who had previously experienced a ≥ 2.0 $\log_{10}$ reduction in HCV RNA after 12 weeks of peginterferon and ribavirin treatment but failed to achieve SVR.[14] The study enrolled both previous non-responders (decline in HCV RNA by ≥ 2 $\log_{10}$ by treatment week 12 but with detectable HCV RNA during the therapy period) and previous relapsers (undetectable HCV RNA at the end of treatment and a subsequent detectable HCV RNA during follow-up). Patients with a previous "null response" to peginterferon and ribavirin were excluded. Treatment with PegIntron® and ribavirin for 48 weeks was compared with two treatment regimens containing boceprevir 800 mg TID: RGT and fixed-duration therapy. Peginterferon and ribavirin were administered for the first 4 weeks – the PR lead-in period – prior to adding boceprevir. The results from this study showed that the addition of boceprevir to peginterferon and ribavirin significantly increased the SVR rate compared with standard treatment with peginterferon and ribavirin alone, and supported the use of early on-treatment response to determine treatment duration.

7.1.3 Additional Phase 2/3 Studies

- Phase 3 study in treatment-failure patients evaluating the efficacy of peginterferon alfa-2a (Pegasys®) in combination with boceprevir and ribavirin (P05685): This Phase 3 study was conducted in CHC genotype 1 patients who had previously experienced ≥ 2.0 $\log_{10}$ reduction in HCV RNA after 12 weeks of peginterferon and ribavirin treatment but failed to achieve SVR and evaluated the safety and efficacy of boceprevir when administered with peginterferon alfa-2a and ribavirin. The study confirmed the safety and efficacy of boceprevir when added to peginterferon alfa-2a and ribavirin.

- Phase 3 single-arm study of boceprevir (PROVIDE; P05514): This study is providing boceprevir treatment to patients who failed to achieve SVR on peginterferon and ribavirin alone in a control arm of another boceprevir study.

- Long-term follow-up study (P05063): The durability of virologic response in subjects with CHC who achieve sustained virologic responders in a previous boceprevir study is being evaluated in an ongoing long-term follow-up study (P05063). Subjects are followed for 3.5 years after the end of treatment (EOT) in the previous boceprevir study. To date, none of the sustained virologic responders enrolled in this study (N=290) has had HCV RNA virology results that met the study criteria for relapse.

- Other ongoing Phase 2 and Phase 3 studies are also included in Table 1.

Table 1 Description of Phase 2 and Phase 3 Clinical Efficacy Studies

Study No. Status	Study Population	Key Elements of Study Design Planned Treatment Duration	Treatment Regimen	No. of Subjects Randomized/Treated
Phase 2 Dose-Finding Study				
P03659 (RESPOND-1) Completed	Previous PEG/RBV Treatment Failures	• Phase 2, double-blind (for RBV), placebo-controlled study to determine the safe and effective dose range of boceprevir (100 to 800 mg) and PEG2b with or without RBV. • Up to 49-wk treatment duration.	BOC (or placebo) 100, 200, 400, or 800 mg PO TID PEG2b 1.5 µg/kg QW RBV (or placebo) 800 to 1400 mg/day	357/357
Phase 2 Study Demonstrating Efficacy and Safety with Proposed Dose of Boceprevir				
P03523 (SPRINT-1) Completed	Treatment-naïve	• Phase 2, open-label, two-part study. • Part 1 included five treatment arms with BOC/PR for 28 or 48 weeks, with and without a 4-week PR lead-in. • Part 2 included exploration of BOC/P/low-dose RBV (400 to 1000 mg/day) for 48 weeks. • Randomization was stratified by race (black vs non-black) and by cirrhosis vs no cirrhosis (Part 1).	Part 1 BOC 800 mg TID PEG2b 1.5 µg/kg QW RBV 800 to 1400 mg/day Part 2 BOC 800 mg TID PEG2b 1.5 µg/kg QW RBV 600 to 1000 mg/day	Total: 598/595 Part 1: 520 treated Part 2: 75 treated
Pivotal Phase 3 Studies				
P05216 (SPRINT-2) Completed	Treatment-naïve	• Phase 3, double-blind, placebo-controlled study comparing two regimens of boceprevir (RGT and BOC/PR (48 wk)) to PR (48 wk). • 2 cohorts: Cohort 1 (non-black) and Cohort 2 (black) • Randomization to 3 treatment arms (1:1:1) in each cohort. • Stratified by HCV genotype 1a vs 1b and by viral load (≤400,000 IU/mL vs >400,000 IU/mL) within cohort. • 28- or 48-wk treatment duration; 4-week lead-in with PR.	BOC 800 mg TID (or placebo) PEG2b 1.5 µg/kg QW RBV 600 to 1400 mg/day	1099/1097 Cohort 1: 938 non-black treated subjects Cohort 2: 159 black treated subjects

Table 1 Description of Phase 2 and Phase 3 Clinical Efficacy Studies

Study No. Status	Study Population	Key Elements of Study Design Planned Treatment Duration	Treatment Regimen	No. of Subjects Randomized/Treated
P05101 (RESPOND-2) Completed	Previous PEG/RBV Treatment Failures	• Phase 3, double-blind, placebo-controlled study comparing two regimens of boceprevir (RGT and BOC/PR (48 wk)) to PR (48 wk). • Randomization to 3 treatment arms in a 1:2:2 ratio. • Stratified by previous treatment response in qualifying treatment regimen and by HCV genotype 1a vs 1b. • 36- or 48-wk treatment duration; 4-week lead-in with PR.	BOC 800 mg TID (or placebo) PEG2b 1.5 µg/kg QW RBV 600 to 1400 mg/day	404/403
Ongoing/Newly Completed Phase 2/3 Studies				
P05685 Completed	Previous PEG/RBV Treatment Failures	• Phase 3, double-blind, placebo-controlled study using boceprevir and PEG2a plus RBV • Stratified by detectable vs undetectable HCV-RNA in qualifying treatment regimen and by HCV genotype 1a vs 1b • 48-wk treatment duration	BOC (or placebo) PEG2a RBV 1000 to 1200 mg/day	202/201
P06086 Ongoing	Treatment-Naïve	• Phase 3, open-label study to compare the effect on efficacy of erythropoietin use vs RBV dose reduction for the management of anemia • Stratified by time to development of anemia and by race (black vs non-black) • 48-wk treatment duration	BOC PEG2b RBV 600 to 1400 mg/day Erythropoietin 40,000 Units SC QW	660 subjects planned
P05411 Ongoing	HCV-Treatment Naïve; coinfected with HIV and HCV-1	• Phase 2, double-blind, placebo-controlled study using BOC/PR in HCV/HIV coinfected subjects • Stratified by cirrhosis/fibrosis vs no cirrhosis/ fibrosis and by viral load • 48-wk treatment duration	BOC (or placebo) PEG2b RBV 600 to 1400 mg/day	99 subjects planned
P05514 (PROVIDE) Ongoing	Previous PEG/RBV Treatment Failures	• Non-pivotal Phase 3 single-arm study to provide boceprevir treatment to subjects who completed per-protocol defined treatment in another boceprevir study and did not achieve SVR while in the peginterferon/RBV control arm • 44- or 48-wk treatment duration	BOC PEG2b RBV 600 to 1400 mg/day	No planned sample size

Table 1 Description of Phase 2 and Phase 3 Clinical Efficacy Studies

Study No. Status	Study Population	Key Elements of Study Design Planned Treatment Duration	Treatment Regimen	No. of Subjects Randomized/Treated
Long-Term Follow-up Study				
P05063 Ongoing	Received at least one dose in a previous Phase 1, 2, or 3 BOC trial	• 3.5-year long-term follow-up study to confirm durability of virologic response, characterize long-term safety, and characterize natural history of HCV sequence variants.	No drug therapy administered	No planned sample size

WBD = weight-based dosing; QW = once a week

7.2 Terminology and Key Concepts

7.2.1 Treatment Response Terminology

The following terms were used to describe treatment response in the pivotal Phase 3 studies.

- **Sustained Virologic Response (SVR):** SVR was defined as undetectable HCV-RNA levels 24 weeks after completion of therapy.
- **Treatment Failure:** Patients who do not attain SVR after a course of therapy are defined as having treatment failure.

7.2.2 Futility Rules

Data from clinical studies of peginterferon and ribavirin have shown that on-treatment HCV RNA measurements can predict the likelihood of SVR. It is generally recommended that PR treatment should be stopped for futility in patients who do not achieve undetectable HCV RNA by TW 24 (treatment-naïve patients) or TW 12 (patients who have failed previous PR treatment).

Futility rules were implemented in the Phase 3 program consistent with the U.S. label for the dosage and administration of PegIntron®. In the Phase 3 study conducted in treatment-naïve patients (SPRINT-2), a TW 24 futility rule was implemented, whereby patients with detectable HCV-RNA at TW 24 discontinued all therapy. In the Phase 3 study conducted in patients who had failed previous treatment (RESPOND-2), the futility rule was implemented at Week 12, whereby patients with detectable HCV-RNA at TW 12 discontinued therapy.

7.2.3 Lead-in Period

The boceprevir Phase 3 program featured a unique concept of initiating therapy with peginterferon and ribavirin for the first 4 weeks – the PR lead in period – prior to adding boceprevir. (Note: The 4 week PR lead-in is a component of the proposed

dosing and administration for boceprevir.) There are several advantages of the PR lead-in:

1. This strategy may reduce the likelihood of the emergence of RAVs by reducing viral levels before the addition of boceprevir. Although viral resistance may develop to boceprevir, it is widely accepted that viral resistance does not develop to either interferon or ribavirin. Adding boceprevir after the steady state concentration of ribavirin is reached and interferon activity is fully realized avoids functional monotherapy and reduces the overall viral load at the introduction of boceprevir. This could lead to a quantitative decrease in the risk of developing viral resistance.
2. The lead-in approach limits boceprevir treatment to those patients who were able to tolerate the first 4-weeks of peginterferon and ribavirin therapy.

7.2.4 Interferon Responsiveness at Treatment Week 4

The PR lead-in period permitted a real-time assessment of interferon responsiveness at Treatment Week 4 (TW 4) - prior to initiation of boceprevir therapy. Interferon responsiveness has previously been shown to be a strong predictor of SVR with peginterferon and ribavirin therapy.

The following terms were used to characterize the virologic response to peginterferon plus ribavirin (PR) alone (the TW 4 Response) in the pivotal Phase 3 clinical studies:

- **Poorly Interferon Responsive:** Patients with a <1.0 $\log_{10}$ decrease in HCV RNA levels from baseline after 4 weeks of PR.

- **Interferon Responsive:** Patients with a ≥1.0 $\log_{10}$ decrease in HCV RNA levels from baseline after 4 weeks of PR.

Analysis of data from the pivotal Phase 3 studies supports the prognostic value (for SVR) of the TW 4 assessment as a direct measure of interferon responsiveness (see Section 8.2.7 and 8.3.7). Analyses also show a strong correlation between poor interferon responsiveness (as defined at TW 4) and "null response" as defined by <2 $\log_{10}$ decline in HCV RNA levels from baseline at TW 12 (see Section 8.4).

7.2.5 Response Guided Therapy

Several clinical studies of peginterferon and ribavirin in genotype 1 CHC suggest that some patients with early on-treatment responses may be effectively treated with less than 48 weeks of therapy. With the addition of boceprevir to standard of care, the boceprevir Phase 3 program was designed to determine if less than 48-weeks of *triple therapy* might be appropriate in selected genotype 1 CHC patients.

The concept of using early on-treatment response to guide treatment duration was incorporated in the design of the pivotal Phase 3 studies using a response-guided therapy (RGT) algorithm. The pivotal Phase 3 studies included three treatment

arms: (1) 48-weeks of PR as the standard of care control arm (PR48); (2) a boceprevir response-guided treatment (RGT) arm; and (3) boceprevir added to a standard 48-week course of PR (BOC/PR48) (the latter as recommended at the FDA Antiviral Drugs Advisory Committee meeting to discuss design issues in the development of products for treatment of chronic Hepatitis C held October 2006).

Choice of TW 8 response to identify patients appropriate for shorter durations of treatment

To determine if patients could be identified who would respond to shorter durations of boceprevir treatment, results from the Phase 2 boceprevir study in treatment-naïve patients (SPRINT-1) were analyzed. Two arms in this study compared 28-week or 48-week regimens of boceprevir added to a similar duration of PR. An analysis of SVR rates by time to first undetectable HCV RNA in the 28-week vs 48-week arms showed that shorter treatment duration was about equally effective with respect to SVR in patients whose first undetectable HCV RNA result occurred at or before TW 8. In contrast, longer treatment duration only offered a substantial advantage with respect to SVR in patients whose first undetectable HCV RNA result occurred after TW 8 (Table 2). Therefore, in the Phase 3 boceprevir RGT treatment arms, patients were identified for shorter duration of therapy depending on whether or not HCV RNA levels were undetectable by TW 8 (i.e., after 4 weeks of boceprevir therapy).

Table 2 Sustained Virologic Response by Time to First Undetectable HCV RNA, SPRINT-1

Protocol No. P03523

Time to First Undetectable HCV-RNA	SVR, % (n/N)	
	BOC/PR28 n=103	BOC/PR48 n=103
TW 2	67 (2/3)	100 (4/4)
TW 4	100 (1/1)	100 (5/5)
TW 6	91 (30/33)	95 (37/39)
TW 8	72 (21/29)	89 (16/18)
TW 10	33 (3/9)	82 (9/11)
TW 12	20 (1/5)	67 (4/6)
TW 16	0 (0/5)	100 (2/2)
TW 20	0/0	0/0
TW 24	0/0	0 (0/1)
TW 28	0 (0/1)	0/0
TW 42	0/0	0/0
Never	0 (0/17)	0 (0/17)

BOC/PR28 = PR lead-in, then BOC/PR for 24 weeks; BOC/PR48 = PR lead-in, then BOC/PR for 44 weeks

Early/Late Responder terminology

The following terms were used to characterize early and late responders in the pivotal Phase 3 studies:

- **Early Responders:** Patients with undetectable HCV RNA level at TW 8.
- **Late Responders:** Patients with a first undetectable HCV RNA level after TW 8.

SVR rates among Early/Late Responders: RGT compared to BOC/PR48

In each of the pivotal Phase 3 studies, a comparison of SVR rates between the two boceprevir regimens (RGT and BOC/PR48) was conducted in order to answer two questions: 1) is short therapy as good as long therapy for patients who are early responders, and 2) is there an added benefit to continuing boceprevir during the extended therapy with peginterferon and ribavirin for late responders.

For the purpose of this comparison, the SVR rates in the RGT treatment arm were assessed in two different ways:

1. An analysis that includes patients with assigned treatment duration by the interactive voice response system (IVRS) (per protocol criteria). In this analysis, patients who discontinued treatment for any reason (e.g., futility) prior to the IVRS assignment of treatment duration (TW 28 in SPRINT-2; TW 36 in RESPOND-2) are not included. To compare SVR rates between the two boceprevir regimens, SVR rates were derived for corresponding patients in the BOC/PR48 arms. (See Sections 8.2.8 and 8.3.8).
2. An analysis that includes all patients with HCV RNA results (undetectable or detectable) at TW 8, regardless of events after TW 8 (e.g., discontinuation due to futility). Patients with missing TW 8 HCV RNA results are not included in this analysis. (See Sections 8.2.9 and 8.3.9).

These two analyses are complementary:

- This first analysis compares RGT to BOC/PR48 among patients who reach the timepoint when RGT is implemented (TW 28 in SPRINT-2; TW 36 in RESPOND-2).
- The second analysis compares RGT to BOC/PR48 based on TW 8 HCV RNA results (undetectable or detectable).

The conclusions from both analyses are the same: short therapy (4-week lead-in, followed by 24 weeks triple therapy in treatment-naïve patients; 4-week lead-in

followed by 32 weeks triple therapy in previous treatment failures) provides robust efficacy for early responders, i.e., those patients with undetectable HCV-RNA by TW 8. For late responders, there is no additional benefit in continuing boceprevir during the extended therapy period.

7.3 Methods

7.3.1 Pivotal Phase 3 Study Designs

7.3.1.1 SPRINT-2

SPRINT-2 was a multi-center, double-blind, randomized (1:1:1 ratio), placebo-controlled pivotal Phase 3 study comparing standard therapy with 48-weeks PR (control) to 2 experimental boceprevir treatment regimens in previously untreated adult patients (≥18 years of age) with CHC genotype 1 infection and HCV RNA ≥10,000 IU/mL. Eligible patients had to have a liver biopsy (obtained within 3 years prior to enrollment) with histology consistent with CHC and no other etiology.

Exclusion criteria included: significant liver disease of other etiology; decompensated liver disease (including but not limited to history or presence of ascites; bleeding varices, or hepatic encephalopathy); HIV or hepatitis B co-infection; uncontrolled diabetes; uncontrolled psychiatric disorder; and active substance abuse.

Because of the marked differences in SVR rates with peginterferon and ribavirin between black and non-black patients, patients were enrolled into two cohorts based on self-identified race: Cohort 1 for non-black patients and Cohort 2 for black patients. Within Cohort 1 and Cohort 2, randomized treatment assignment was stratified based on baseline viral load: high viral load (>400,000 IU/mL) versus low viral load (≤400,000 IU/mL) (based on screening visit HCV RNA results) and on HCV genotype 1a infection versus HCV genotype 1b infection (based on screening visit TRUGENE assay results). Data are presented for the combined population, as well as each cohort separately.

Patients were randomized (1:1:1) to the following 3 treatment arms:

- PR48 (standard of care): Patients received 48 weeks of peginterferon alfa-2b 1.5 µg/kg administered subcutaneously weekly and oral ribavirin using weight-based dosing from 600 to 1400 mg/day divided BID, plus placebo TID after the 4-week PR lead-in.

- RGT (response-guided therapy): Patients received peginterferon and ribavirin for a 4-week lead-in period, followed by the addition of boceprevir.

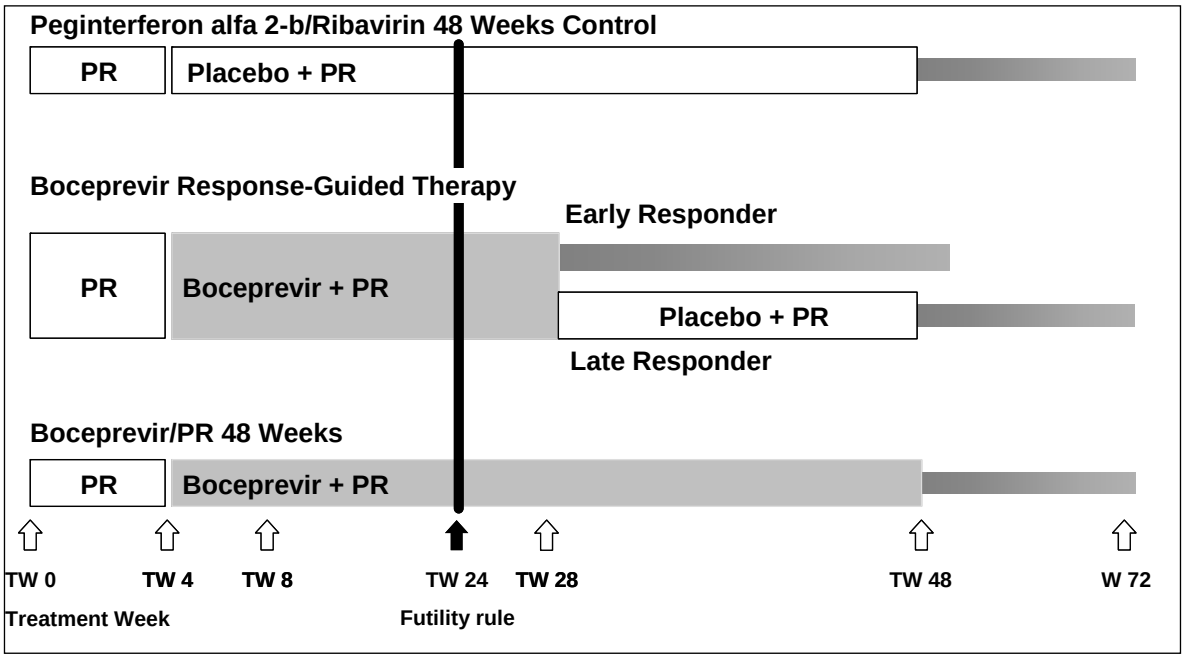
    - Patients were treated for a total duration of 28 or 48 weeks, depending on whether or not their HCV RNA levels were undetectable from TW 8 through TW 24. An interactive voice response system (IVRS) assigned patients to one of the following two groups at TW 28:

- Patients with undetectable HCV RNA at TW 8 through TW 24 stopped all therapy at TW 28 (early responders).
- Patients with detectable HCV RNA at TW 8 or at any visit *up to* TW 24 stopped boceprevir at TW 28 and continued to receive peginterferon and ribavirin plus placebo from TW 28 to TW 48 (late responders).

- BOC/PR48 (fixed-duration therapy): Patients received peginterferon and ribavirin for a 4-week lead-in period, followed by the addition of boceprevir for 44 weeks.

In all arms, patients with detectable HCV RNA at TW 24 discontinued all treatment for futility. Four boceprevir 200 mg capsules or matching placebos were to be taken with a snack TID. All patients were followed through study week 72 (Figure 1).

Figure 1 SPRINT-2 Study Design



7.3.1.2 RESPOND-2

RESPOND-2 was a multi-center, double-blind, randomized (1:2:2 ratio), placebo-controlled pivotal Phase 3 study comparing standard PR therapy (control) with 2 experimental boceprevir treatment regimens in adult patients (≥18 years of age) with CHC genotype 1 infection who had demonstrated responsiveness to interferon (minimum duration of therapy 12 weeks) but failed to achieve SVR on a previous PR treatment.

To be eligible for enrollment, during the qualifying (previous) treatment regimen, patients must have had either:

- a decline in HCV RNA by ≥ 2 $\log_{10}$ by treatment week 12 but with a detectable HCV RNA during the therapy period (non-responder) or
- undetectable HCV RNA at the end of treatment and a subsequent detectable HCV RNA during follow-up (relapser)

Patients with a previous "null response" to peginterferon and ribavirin were not eligible for enrollment. Eligible patients had to have a liver biopsy (obtained within 3 years prior to enrollment) with histology consistent with CHC and no other etiology. Other exclusion criteria were similar to those in SPRINT-2.

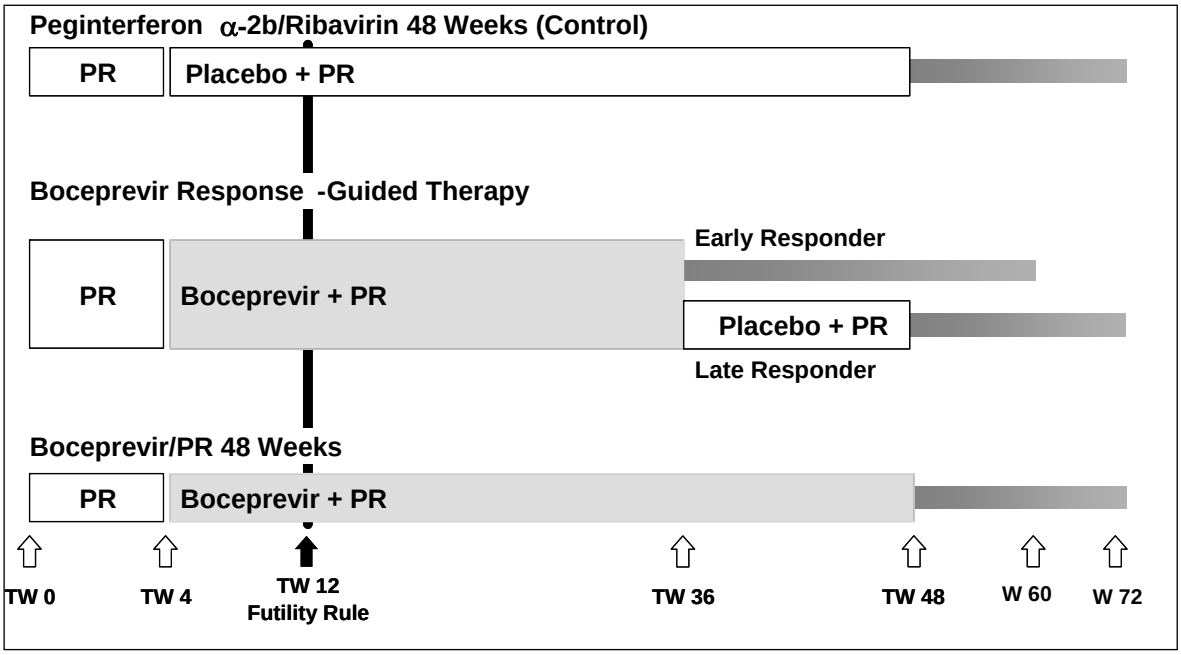
Randomized treatment assignment was stratified based on the patient's previous response to therapy (non-responder or relapser) and on HCV genotype (1a or 1b infection) as determined by the TRUGENE assay.

Patients were randomized (1:2:2) to the following 3 treatment arms:

- PR48 (standard of care): Patients received 48 weeks of peginterferon alfa-2b 1.5 µg/kg administered subcutaneously weekly and oral ribavirin using weight-based dosing from 600 to 1400 mg/day divided BID, plus placebo TID after the 4-week PR lead-in.
- RGT (response-guided therapy): Patients received peginterferon and ribavirin for a 4-week lead-in period, followed by the addition of boceprevir.
  - Patients were treated for a total duration of 36 or 48 weeks, depending on whether or not their HCV RNA level was undetectable at TW 8. An interactive voice response system (IVRS) assigned patients to one of the following two groups at TW 36:
    - Patients with undetectable HCV RNA at TW 8 stopped all therapy at TW 36 (early responders).
    - Patients with detectable HCV RNA at TW 8 stopped boceprevir at TW 36 and continued to receive peginterferon and ribavirin plus placebo from TW 36 to TW 48 (late responders).
- BOC/PR48 (fixed-duration therapy): Patients received peginterferon and ribavirin for a 4-week lead-in period, followed by the addition of oral boceprevir 800 mg TID for 44 weeks.

In all arms, patients with detectable HCV RNA at TW 12 discontinued all treatment for futility. All patients were followed through study week 72 (Figure 2).

Figure 2 RESPOND-2 Study Design



7.3.1.3 HCV RNA and HCV Genotype Assays

In the pivotal Phase 3 studies, HCV RNA was measured using the TaqMan 2.0 assay (Roche Diagnostics) with a lower limit of detection (LOD) of 9.3 IU/mL and limit of quantitation (LOQ) of 25 IU/mL. HCV RNA assessments at all on-treatment decision timepoints were based on LOD.

In the per protocol analysis, SVR was determined using the LOD of the assay to assess HCV RNA levels at follow-up timepoints. At the request of the FDA, a post-hoc analysis of SVR using HCV RNA <25 IU/mL as a surrogate for "undetectable HCV RNA" at follow-up timepoints was also calculated.

The subtype of genotype 1 HCV was determined by the TRUGENE assay (Bayer Diagnostics) for randomization, and then subsequently by sequencing the NS5B region (Virco).

7.3.1.4 Liver Histology

In order to be eligible for enrollment in the pivotal Phase 3 studies, patients had to have a liver biopsy (obtained within 3 years prior to enrollment) with histology consistent with CHC and no other etiology. Eligibility and baseline cirrhosis were determined by the investigator based upon the local pathology report. (Note: Patients with decompensated cirrhosis were not eligible to enroll in the pivotal Phase 3 studies.)

Liver biopsies were subsequently read by a single treatment-blinded pathologist who assigned METAVIR fibrosis and steatosis scores. A METAVIR F3 score indicates

bridging fibrosis, and a METAVIR F4 score indicates cirrhosis or advanced fibrosis of the liver. Subgroup analyses were conducted based on the investigator assessment of cirrhosis at enrollment as well as on the METAVIR fibrosis score as read by the central pathologist.

7.3.2 Phase 3 Statistical Methodology

The pivotal Phase 3 studies were designed as superiority studies to detect significant differences in sustained virologic response (SVR) rates between either of the two boceprevir regimens (RGT or BOC/PR48) and standard of care (PR48). SVR was defined as undetectable HCV RNA 24 weeks after completion of therapy. SVR is an objective validated measure of response, and is an established endpoint that has been used in the licensing of all current anti-HCV therapies.

The primary efficacy objective was to compare the two boceprevir arms with the control arm in all patients who received ≥1 dose of any study medication (i.e., the first dose of the PR lead-in); the full analysis set population (FAS). The key secondary efficacy objective was to compare the two boceprevir arms with the control arm in patients who received ≥1 dose of boceprevir (experimental arms) or placebo (control arm) (modified intent to treat population [mITT]). To account for multiplicity between the primary and key secondary analyses, the key secondary analyses were only conducted if the significance of the primary comparisons was established.

For the per protocol primary and key secondary analyses, the SVR rates were based on the last observation carried forward (LOCF) approach, in which the follow-up week (FW) 12 HCV RNA result was carried forward for patients with missing HCV RNA value at and after FW 24. Of note, this was an extremely rare event. The limit of detection (LOD) of the HCV RNA assay (9.3 IU/mL) was used for all on-treatment and end-of-treatment (EOT) timepoints and for the per protocol determination of SVR rates.

The end of treatment response was based on undetectable HCV RNA levels at EOT regardless of treatment duration. Relapse was evaluated as the proportion of patients with undetectable HCV RNA at EOT and detectable HCV RNA at the end of follow-up (EOF) among patients who had undetectable HCV RNA at EOT and were not missing EOF data.

All statistical comparisons for the primary and key secondary efficacy analyses were carried out using a two-sided Cochran-Mantel Haenszel (CMH) chi-square test adjusted for baseline stratification factors (RESPOND-2), and adjusted for the two cohorts as well as the baseline stratification factors for the combined analysis of Cohort 1 and Cohort 2 (SPRINT-2). (Note: For SPRINT-2, the primary efficacy analysis was the overall [stratified] analysis of the FAS, which combined the results for Cohort 1 and Cohort 2.)

In order to control the type 1 error for the comparisons of the two boceprevir-containing treatment arms to 48-weeks PR standard of care, a step down approach

was used. BOC/PR48 was first compared against PR48. If the p-value was <0.05, superiority of BOC/PR48 over PR48 standard therapy was concluded and the next comparison for the RGT regimen was carried out (RGT vs. PR48). If this p-value was <0.05, superiority of boceprevir RGT over standard therapy was concluded. A similar step-down approach was used to control the type 1 error for the key secondary analysis.

A logistic regression model with SVR as the dependent variable was fit using treatment assignment, stratification factors, baseline disease characteristics, and other known prognostic factors as independent variables, to identify predictors of SVR. Logistic regression analyses were also conducted within each treatment arm. Both univariate and multivariable models (full model and stepwise selection method) were used to make these evaluations. A separate logistic regression model including on-treatment response and baseline factors was used to assess the impact of early response on SVR.

The association between interferon responsiveness (after the 4-week PR lead-in) and SVR was assessed by summarizing the change from baseline in the $\log_{10}$ HCV RNA at TW 4 (<1 $\log_{10}$ decline in HCV RNA or ≥ 1 $\log_{10}$ decline in HCV RNA) and the SVR rate. Of note, the TW 4 response can be considered a baseline factor because it is obtained before the addition of boceprevir (or boceprevir placebo).

At the request of the FDA, a post-hoc analysis of SVR using HCV RNA <25 IU/mL as a surrogate for "undetectable HCV RNA" at follow-up timepoints (rather than the LOD of the assay [9.3 IU/mL]) was also conducted.

8.0 EFFICACY

8.1 Overview

The pivotal Phase 3 studies provide substantial evidence of the clinical efficacy of boceprevir used in combination with peginterferon and ribavirin in the treatment of CHC genotype 1 infection. The following is summary of the efficacy results of these studies:

- In **SPRINT-2** (treatment-naive), boceprevir demonstrated a significant increase in SVR rates in both boceprevir-containing treatment arms compared to control: 63% RGT, 66% BOC/PR48 vs. 38% PR48 control (full analysis set [FAS], p<0.0001 for both comparisons). Efficacy was also shown in the cohort of black patients: 42% RGT, 53% BOC/PR48 vs. 23% PR48 (FAS, p=0.044 and p=0.004, respectively) and in the cohort of non-black patients: 67% RGT, 68% BOC/PR48 vs. 40% PR48 control (FAS, p<0.0001 for both comparisons).
- **RESPOND-2** (previous PR treatment failure) demonstrated a significant increase in SVR for both boceprevir-containing treatment arms compared to control: 59% RGT, 66% BOC/PR48 vs. 21% PR48 control (FAS; p<0.0001 for both comparisons).

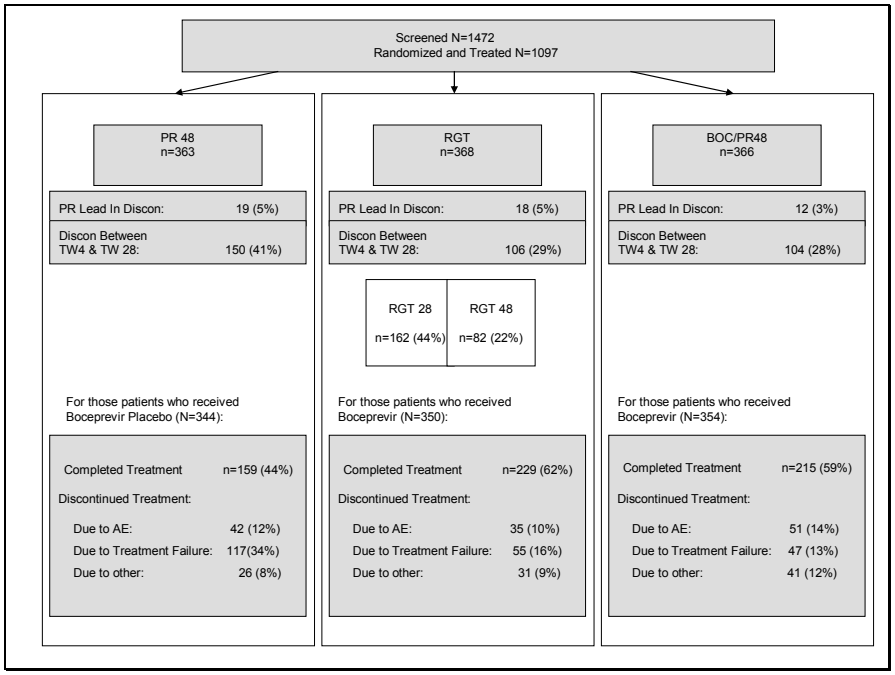
In both Phase 3 studies, RGT was shown to be an effective treatment paradigm, offering shorter therapy for many patients. The addition of boceprevir to PR resulted in increased SVR rates in all subpopulations, including patients with poor interferon responsiveness (<1.0 log_{10} decline in HCV RNA after the 4-week PR lead in) and blacks.

8.2 Efficacy in SPRINT-2

8.2.1 Disposition

Figure 3 displays the disposition of all screened patients in SPRINT-2. A total of 1246 and 226 patients were screened for Cohort 1 and 2, respectively, of whom 940 non-black and 159 black patients were randomized. Other than 2 patients in Cohort 1, all randomized patients were treated with ≥1 dose of study medication. Forty-nine patients (4%) discontinued PR during the lead-in period, and never received boceprevir or placebo. Discontinuations for futility at Week 24 occurred in 108 (30%), 33 (9%), and 28 (10%) of patients in the PR48, RGT, and BOC/PR48 arms, respectively.

Figure 3 Disposition of Patients in SPRINT-2



8.2.2 Patient Demographics

Demographics and baseline characteristics were similar across the three treatment arms within each cohort (Table 3). Overall, 92% of patients had HCV RNA levels >400,000 IU/mL and 9% of patients had bridging fibrosis or cirrhosis (METAVIR

F3/4). Black patients tended to be heavier and were more often infected with HCV subtype 1a than non-black patients.

Table 3 Demographics and Baseline Characteristics, SPRINT-2

Protocol No. 05216

	Number (%) of Patients, FAS					
	Cohort 1 (Non-Black)			Cohort 2 (Black)		
	PR48 n=311	RGT n=316	BOC/PR48 n=311	PR48 n=52	RGT n=52	BOC/PR48 n=55
Sex, n (%)						
Female	140 (45)	116 (37)	123 (40)	17 (33)	23 (44)	22 (40)
Male	171 (55)	200 (63)	188 (60)	35 (67)	29 (56)	33 (60)
Race, n (%)						
White	296 (95)	304 (96)	295 (95)	--	--	--
Black	--	--	--	52 (100)	52 (100)	55 (100)
Asian	9 (3)	4 (1)	8 (3)	--	--	--
Other	6 (2)	8 (3)	8 (3)	--	--	--
Region, n (%)						
North America	203 (65)	228 (72)	218 (70)	51 (98)	51 (98)	52 (95)
Europe	98 (32)	78 (25)	83 (27)	1 (2)	1(2)	3 (5)
Latin America	9 (3)	10 (3)	10 (3)	0 (0)	0 (0)	0 (0)
Age (y)						
Mean (SD)	48.3 (10.3)	49.4 (9.4)	48.5 (9.0)	50.5 (8.5)	52.4 (7.9)	50.9 (7.0)
BMI						
Mean (SD)	26.9 (4.5)	27.6 (4.9)	27.4 (5.2)	29.3 (4.4)	29.4 (5.2)	31.0 (6.0)
Viral Load (IU/mL)						
≤400,000	26 (8)	29 (9)	23 (7)	0	3 (6)	2 (4)
>400,000	285 (92)	287 (91)	288 (93)	52 (100)	49 (94)	53 (96)
HCV Subtype (TRUGENE), n(%)						
1a	144 (46)	144 (46)	153 (49)	33 (63)	35 (67)	34 (62)
1b	114 (37)	120 (38)	117 (38)	12 (23)	14 (27)	16 (29)
1 (subtype unknown)	53 (17)	52 (16)	41 (13)	7 (13)	3 (6)	5 (9)

Table 3 Demographics and Baseline Characteristics, SPRINT-2

Protocol No. 05216

	Number (%) of Patients, FAS					
	Cohort 1 (Non-Black)			Cohort 2 (Black)		
	PR48 n=311	RGT n=316	BOC/PR48 n=311	PR48 n=52	RGT n=52	BOC/PR48 n=55
METAVIR Fibrosis Score, n (%)						
F0/1/2	277 (89)	279 (88)	265 (85)	51 (98)	40 (77)	48 (87)
F3/4	23 (7)	26 (8)	36 (12)	1 (2)	8 (15)	6 (11)

8.2.3 Primary Efficacy Endpoint – Sustained Virologic Response

In the overall analysis, which combined Cohort 1 and Cohort 2, the SVR rates were statistically significantly higher in patients receiving a boceprevir-containing regimen compared to standard of care alone: 63% RGT, 66% BOC/PR48, vs. 38% PR48 control (FAS, p<0.0001 for both comparisons) (Table 4).

The high SVR rates in patients receiving a boceprevir-containing regimen were primarily driven by higher rates of undetectable HCV RNA at the End-of-Treatment (EOT) compared with control. In addition, relapse rates were substantially lower in the boceprevir-containing arms (9%) than in the PR48 control arm (22%).

Table 4 Sustained Virologic Response in the FAS Population, SPRINT-2

Protocol No. P05216

	Control	Experimental	
	PR48 n=363	RGT n=368	BOC/PR48 n=366
SVR, n (%)	137 (37.7)	233 (63.3)	242 (66.1)
Δ SVR (%)	--	25.6	28.4
95%CI for Δ	--	18.6, 32.6	21.4, 35.3
P-value	--	<.0001	<.0001
EOT (Undetectable HCV-RNA), n (%)	191 (52.6)	261 (70.9)	277 (75.7)
Relapse, n/N (%)	39/176 (22.2)	24/257 (9.3)	24/265 (9.1)

In each cohort, SVR rates were also significantly higher in patients receiving a boceprevir-containing regimen compared to control (Table 5). The SVR rates in non-black patients (Cohort 1) were 67% RGT, 68% BOC/PR48 vs. 40% PR48 control (FAS; p<0.0001 for both comparisons). SVR rates in black patients (Cohort 2) were 42% RGT, 53% BOC/PR48 vs. 23% PR48 control (FAS; p=0.044, p=0.0035,

respectively). Consistent with historical response data, overall SVR rates among black patients were lower than in non-black patients randomized to the same treatment arms. However, the advantage of adding boceprevir to PR standard of care in black patients is clearly evident and as great as the advantage seen in other patient groups.

Table 5 Sustained Virologic Response in the FAS Population by Cohort, SPRINT-2

Protocol No. P05216

	Cohort 1 (Non-Black)			Cohort 2 (Black)		
	Control	Experimental		Control	Experimental	
	PR48 n=311	RGT n=316	BOC/PR48 n=311	PR48 n=52	RGT n=52	BOC/PR48 n=55
SVR n (%)	125 (40.2)	211 (66.8)	213 (68.5)	12 (23.1)	22 (42.3)	29 (52.7)
Δ SVR (%)	--	26.6	28.3	--	19.2	29.7
95% CI for Δ	--	19.1, 34.1	20.8, 35.8	--	1.6, 36.9	12.2, 47.1
P value	--	<.0001	<.0001	--	0.0440	0.0035
EOT (Undetectable HCV-RNA) n (%)	176 (56.6)	235 (74.4)	241 (77.5)	15 (28.8)	26 (50.0)	36 (65.5)
Relapse n/N (%)	37/162 (22.8)	21/232 (9.1)	18/230 (7.8)	2/14 (14.3)	3/25 (12.0)	6/35 (17.1)

8.2.4 Sustained Virologic Response in the mITT Population

The mITT analysis included all patients receiving ≥ 1 dose of boceprevir or placebo. This analysis – which excluded patients who dropped out during the 4-week PR lead-in and were never treated with boceprevir (or boceprevir placebo) – was conducted to better understand the impact of boceprevir treatment on SVR. SVR rates were significantly higher in patients receiving a boceprevir-containing regimen compared to control: 67% RGT, 68% BOC/PR48 vs. 40% PR48 control. SVR rates for non-black patients (Cohort 1) were 70% RGT, 71% BPC/PR48 vs. 42% PR48 control ($p<0.0001$ for both comparisons); and for black patients (Cohort 2) were 47% RGT, 53% BOC/PR48 vs. 26% PR48 control ($p=0.037$ and $p=0.011$, respectively) (Table 6).

Table 6 Sustained Virologic Response in the mITT Population by Cohort, SPRINT-2

Protocol No. P05216

	Cohort 1 (Non-Black)			Cohort 2 (Black)		
	Control	Experimental		Control	Experimental	
	PR48 n=297	RGT n=303	BOC/PR48 n=299	PR48 n=47	RGT n=47	BOC/PR48 n=55
SVR n (%)	125 (42.1)	211 (69.6)	213 (71.2)	12 (25.5)	22 (46.8)	29 (52.7)
Δ SVR (%)	--	27.5	29.1	--	21.3	27.2
95% CI for Δ	--	19.9 35.2	21.5, 36.8	--	2.3, 40.2	9.0, 45.3
P value	--	<.0001	<.0001	--	0.0366	0.0107
EOT (Undetectable HCV-RNA) n (%)	176 (59.3)	235 (77.6)	241 (80.6)	15 (31.9)	26 (55.3)	36 (65.5)
Relapse n/N (%)	37/162 (22.8)	21/232 (9.1)	18/230 (7.8)	2/14 (14.3)	3/25 (12.0)	6/35 (17.1)

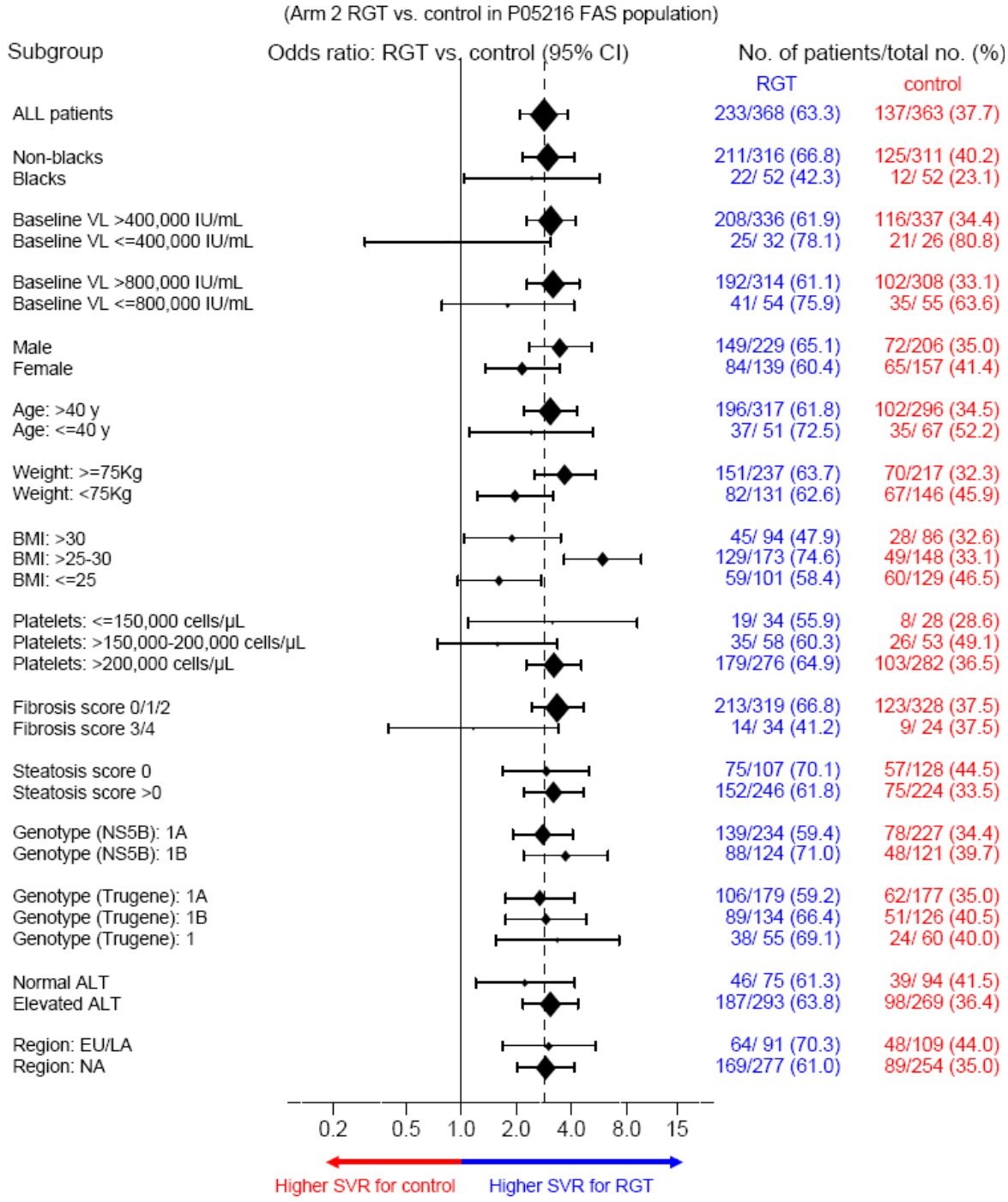
Of note, the numerical difference in SVR rates between the RGT and BOC/PR48 arms in black patients in the FAS analysis (Table 5) is in part due to a higher number of patients in the RGT arm who dropped out during the 4-week PR lead-in (5 patients in the RGT arm compared to no patients in the BOC/PR48 arm). In addition, during the period of identical therapy (4-week PR lead-in followed by 24 weeks of boceprevir, interferon and ribavirin), more patients in the BOC/PR48 arm achieved undetectable HCV RNA than in the RGT arm.

8.2.5 Sustained Virologic Response by Baseline Characteristics

Odds ratios (ORs) and corresponding confidence intervals (CIs) for treatment effect (RGT vs PR48 control, Figure 4, and BOC/PR48 vs PR48 control, Figure 5) were computed overall as well as by baseline subgroups. In these forest plots, the OR (diamond, with the size of the diamond proportional to size of the subgroup), and associated CIs are presented along with a solid vertical line at 1.0 indicating no treatment difference, and a dotted vertical line indicating the overall OR. An OR greater than 1.0 indicates advantage of the boceprevir-containing treatment arm over PR control.

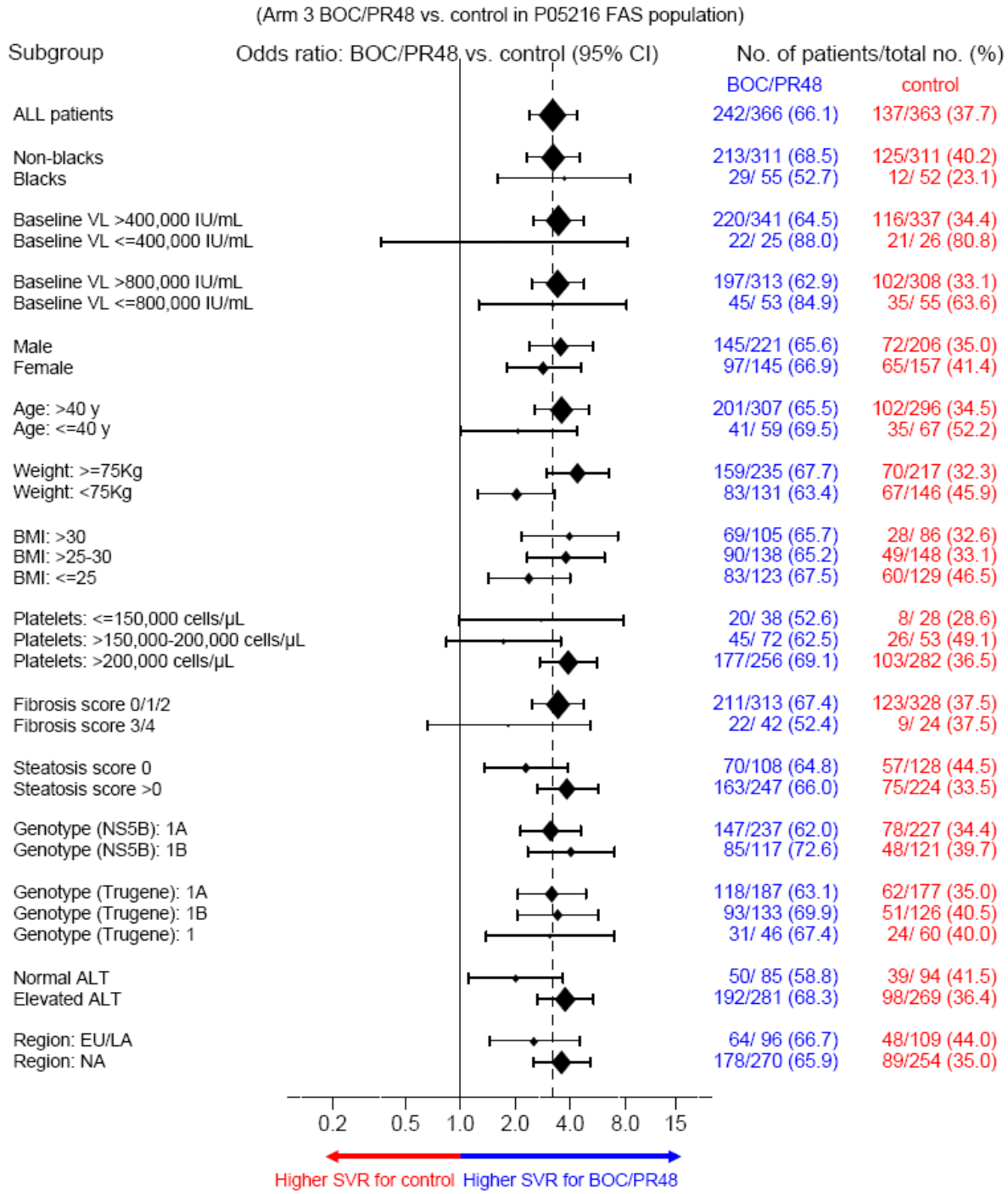
The boceprevir-containing arms had higher SVR rates compared to the PR48 control arm in all key subgroups, demonstrating robustness of the overall treatment effect, as well as consistency of treatment effect across subgroups.

Figure 4 Odds Ratio and 95% Confidence Interval for SVR by Baseline Subgroups: RGT vs PR48 Control (Cohort 1 Plus Cohort 2, FAS; SPRINT-2)



[1]: Forest plot is based on logistic regression of SVR with treatment group as covariate.

Figure 5 Odds Ratio and 95% Confidence Interval for SVR by Baseline Subgroups: BOC/PR48 vs PR48 Control (Cohort 1 Plus Cohort 2, FAS; SPRINT-2)



Forest plot is based on logistic regression of SVR with treatment group as covariate.

8.2.6 Predictors of Sustained Virologic Response

Multivariable logistic regression analyses of the overall study population identified four baseline factors significantly associated with SVR (genotype 1b, non-black race, HCV RNA ≤400,000 IU/mL, and the absence of advanced fibrosis) in addition to treatment allocation to a boceprevir-containing treatment regimen (Table 7). In an expanded model which also included TW 4 response, interferon responsiveness (as defined by ≥1 $\log_{10}$ decline in HCV RNA level at the end of the 4-week PR lead-in) was strongly predictive of attaining SVR (OR = 9.592, p<0.0001).

Table 7 Multivariable Stepwise Logistic Regression for SVR by Baseline Factors, All Treatment Arms for Cohort 1 Plus Cohort 2, SPRINT-2

Protocol No. P05216

Effect[a]	Odds Ratio (95%CI)	Chi Square P-value
Treatment: BOC/PR48 vs Control	3.591(2.607, 4.946)	<0.0001
Treatment: RGT vs Control	3.196 (2.326, 4.392)	<0.0001
Genotype: 1b vs. 1a	1.36 (1.03, 1.79)	0.0318
Race: non-Black vs Black	2.08 (1.44, 3.1))	0.0001
Baseline HCV-RNA: ≤400,000 vs >400,000 IU/mL	3.703 (2.040, 6.722)	<0.0001
Fibrosis: 0/1/2 vs 3/4	1.859 (1.200, 2.880)	0.0055

[a] Covariates included in the model consisted of treatment (BOC/PR48 vs Control, RGT vs Control), genotype (1a vs 1b, by NS5b, Virco), race (Black vs non-Black), baseline HCV RNA (≤400,000 vs >400,000 IU/mL), gender (female vs male), age (≤40 vs >40 years), baseline weight (40-50 vs 105-125 kg, 50-65 vs 105-125 kg, 65-80 vs 105-125 kg, 80-105 vs 105-125 kg), BMI (25-30 vs >30, 20-25 vs >30), baseline platelets (150,000-200,000 vs >200,000/µL, ≤150,000 vs >200,000/µL), baseline fibrosis (0/1/2 vs 3/4), baseline steatosis (0 vs >0), baseline ALT (elevated vs normal), statin use prior to treatment (yes vs no), and region (North America vs Europe/Latin America).

8.2.7 Interferon Responsiveness at Treatment Week 4 and Sustained Virologic Response

The 4-week PR lead-in period allowed an assessment of interferon responsiveness and its relationship to SVR. In all treatment groups, SVR rates were lower in patients with poor interferon responsiveness (<1.0 $\log_{10}$ decline in HCV RNA at TW 4) than in patients with interferon responsiveness (≥1.0 $\log_{10}$ decline in HCV RNA at TW 4). However, SVR rates were consistently higher in the boceprevir-containing treatment arms than in the control arm regardless of whether the TW 4 decline was less than or greater than or equal to 1 $\log_{10}$ (Table 8).

Table 8 Sustained Virologic Response Based on Treatment Week 4 (Lead-in) Response in Treatment-Naïve Patients (FAS), SPRINT-2

Protocol No. P05216

	Control	Experimental	
	PR48 n=363	RGT n=368	BOC/PR48 n=366
SVR by TW 4 Response, n/N (%)			
<1 Log Decline	3/83 (3.6)	27/97 (27.8)	36/95 (37.9)
≥1 Log Decline	133/260 (51.2)	203/252 (80.6)	200/254 (78.7)
Missing HCV-RNA	1/20 (5.0)	3/19 (15.8)	6/17 (35.3)

8.2.8 Sustained Virologic Response in Early and Late Responders: RGT compared to BOC/PR48

SVR rates in the two boceprevir treatment arms were compared to evaluate the effectiveness of boceprevir response-guided therapy (RGT) compared to fixed duration therapy (BOC/PR48) in early and late responders.

8.2.8.1 Methods

The following comparisons were conducted:

- Early Responders: SVR rates in the two boceprevir treatment arms (RGT and BOC/PR48) were compared to evaluate whether short treatment duration is as efficacious as 48-week duration among early responders.
  - This analysis included patients who completed 28-weeks and had undetectable HCV RNA level from TW 8 through TW 24 of treatment. Patients in the RGT arm who were assigned by the IVRS to stop therapy at TW 28 (4-weeks PR lead-in followed by 24 weeks of boceprevir plus peginterferon and ribavirin) were compared to patients in the BOC/R48 arm who were to receive 4-weeks PR lead-in followed by 44 weeks of boceprevir plus peginterferon and ribavirin.
- Late responders: SVR rates in the two boceprevir treatment arms (RGT and BOC/PR48) were compared to evaluate whether a total of 48-weeks of boceprevir, peginterferon and ribavirin is needed or whether boceprevir may be stopped and peginterferon and ribavirin used alone for the last 20 weeks among late responders.
  - This analysis included patients who completed 28-weeks of treatment and had their first undetectable HCV RNA after TW 8 or had undetectable HCV RNA at TW 8 but had detectable HCV RNA after TW 8 and before TW 24 (late responders). Patients in the RGT arm who were assigned by the IVRS to complete 48-weeks of treatment (4-weeks lead-in, followed by 24-weeks of peginterferon, ribavirin and boceprevir, followed by 20 weeks peginterferon

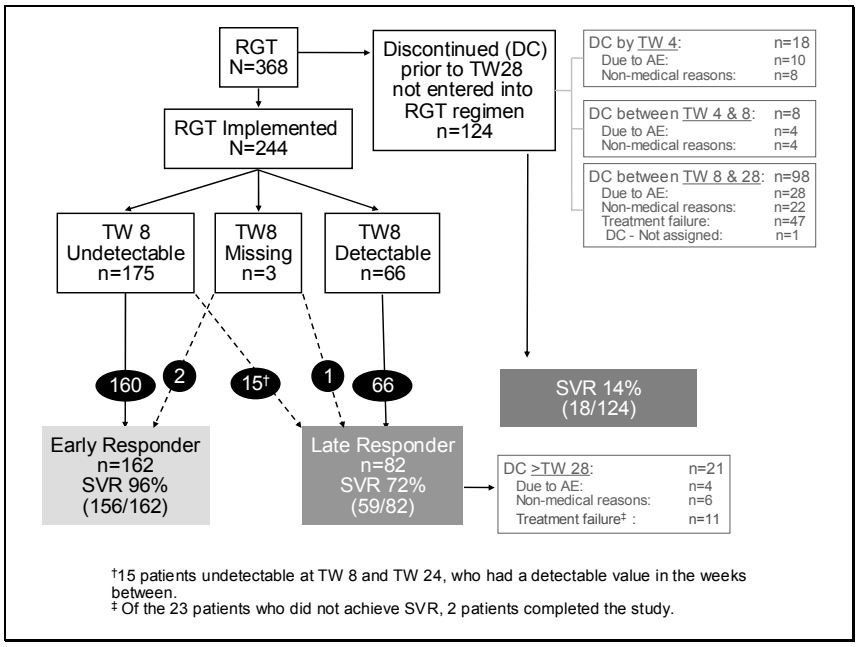
and ribavirin alone) were compared to patients in the BOC/PR48 arm who were to receive 4-weeks lead-in, followed by 44-weeks of peginterferon, ribavirin and boceprevir.

It should be noted that subgroups of early and late responders in the BOC/PR48 arm were identified solely for the purpose of the above comparisons. Patients who discontinued treatment prior to completing TW 28, for any reason, were not included in these analyses. Therefore, as patients in both arms received identical treatment through TW 28, no bias was introduced.

8.2.8.2 Disposition

Of the 368 patients randomized to the RGT arm, 124 patients discontinued prior to TW 28 and were not assigned a treatment duration by the IVRS. A schematic showing the disposition of patients in the RGT arm is presented in Figure 6.

Figure 6 Disposition of Patients in the RGT Arm in SPRINT-2



8.2.8.3 Early Responders

In the RGT arm, a total of 162 patients were assigned to the shorter 28-week treatment duration. In the BOC/PR48 arm, a total of 161 patients served as the corresponding control. Treatment with a 4-week PR lead-in followed by the addition of boceprevir for 24 weeks produced a very high rate of SVR among early responders. SVR rates were 96% both for patients in the RGT arm (completed treatment with 24 weeks of boceprevir and 28 weeks total) and for the corresponding patients in the fixed-duration therapy BOC/PR48 arm (treated with 44 weeks of boceprevir and 48 weeks total) (Table 9). These results strongly support the efficacy of short duration therapy among early responders.

Table 9 Sustained Virologic Response, End of Treatment Response, and Relapse Rates in Boceprevir-containing Arms among Early Responders and Late Responders, SPRINT-2

Protocol No. P05216

	Treatment-Naïve Patients Cohort 1 Plus Cohort 2			
	Early Responders[a]		Late Responders[a]	
	RGT n=162	BOC/PR48 n=161	RGT n=82	BOC/PR48 n=73
SVR	156/162 (96.3)	155/161 (96.3)	59/82 (72.0)	55/73 (75.3)
95% CI	93.4, 99.2	93.3, 99.2	62.2, 81.7	65.5, 85.2
EOT (Undetectable HCV-RNA), n (%)	162/162 (100.0)	159/161 (98.8)	66/82 (80.5)	66/73 (90.4)
Relapse	5/161 (3.1)	2/157 (1.3)	7/66 (10.6)	9/64 (14.1)

a Includes only patients who completed 28 weeks of treatment

8.2.8.4 Late Responders

In the RGT arm, a total of 82 patients were assigned to the 48-week treatment duration. In the BOC/PR48 arm, a total of 73 patients served as the corresponding control. SVR rates were 72% for patients in the RGT arm (treated with 24 weeks of boceprevir and 48 weeks total) and 75% for the corresponding patients given fixed-duration therapy BOC/PR48 (treated with 44 weeks of boceprevir and 48 weeks total) (Table 9). Again, these results provide strong support for the RGT paradigm.

Of note, 15 patients in the RGT arm with undetectable HCV RNA levels at TW 8 had positive HCV RNA results between TW 8 and TW 24 and per protocol were assigned by the IVRS to 48-weeks of therapy (see Figure 6). One of these 15 patients had positive HCV RNA levels at multiple timepoints; the other 14 patients had a single low positive HCV RNA result and retesting of two additional back-up samples from the same timepoint (after the assignment of treatment duration) showed undetectable HCV RNA results. If these 14 patients with a "false positive" HCV RNA result between TW 8 and TW 24 are excluded from the analysis, the SVR rate among late responders in the RGT arm is 66% (45/68).

8.2.9 Sustained Virologic Response Rates Based on Treatment Week 8 HCV RNA Results: RGT compared to BOC/PR48

As discussed in Section 7.2.5, a second approach to comparing RGT and BOC/PR48 is in a patient population defined by TW 8 HCV RNA results (undetectable or detectable).

The proportion of early responders (undetectable HCV RNA at TW 8) was approximately 3.5 times higher in the boceprevir-containing arms (57% in the RGT arm and 56% in the BOC/PR48 arm) compared to the PR control arm (17% PR48).

High SVR rates were seen in early responders (undetectable HCV RNA at TW 8) in both the RGT and BOC/PR48 arms (88% and 90%, respectively) (Table 10). In the RGT arm, most patients with undetectable HCV RNA results at TW 8 were treated for 28 weeks, with the exception of 15 patients who received 48 weeks of therapy (14 had a "false positive" HCV RNA result between TW 8 and TW 24). Comparable but lower SVR rates were seen in patients with detectable HCV RNA results at TW 8 in both the RGT and BOC/PR48 arms (36% and 40%, respectively).

Table 10 Sustained Virologic Response Based on HCV RNA Detectability at Treatment Week 8, SPRINT-2

Protocol No. P05216

	Treatment-Naïve Patients Cohort 1 Plus Cohort 2[a]	
	RGT n=337	BOC/PR48 n=335
SVR by TW 8 Detectability, n/N (%)		
Undetectable	184/208 (88.5)	184/204 (90.2)
Detectable	46/129 (35.7)	52/131 (39.7)

a Includes only patients with HCV RNA results at TW 8.

Of note, the two different analysis approaches (provided in Sections 8.2.8 and 8.2.9) show similar high rates of SVR among early responders. In contrast, the SVR rates among late responders (Section 8.2.8) are higher than the SVR rates among patients with detectable HCV RNA at TW 8 because the latter analysis approach includes all patients with HCV RNA results at TW 8 regardless of whether they discontinued for futility or reached TW 28.

8.2.10 Sustained Virologic Response using HCV RNA <25 IU/mL

Results consistent with the primary efficacy endpoint were obtained when SVR rates were calculated using HCV RNA <25 IU/mL as a surrogate for "undetectable HCV RNA" at follow-up timepoints (rather than the LOD of the assay [9.3 IU/mL]). SVR rates were significantly higher in patients receiving a boceprevir-containing regimen compared to control: 63% RGT, 66% BOC/PR48, 38% PR48 control (FAS, Cohort 1 + Cohort 2). Only one patient (non-black, PR48 control), who was considered a non-SVR in the primary efficacy analysis, was categorized as having achieved SVR using HCV RNA < 25 IU/mL.

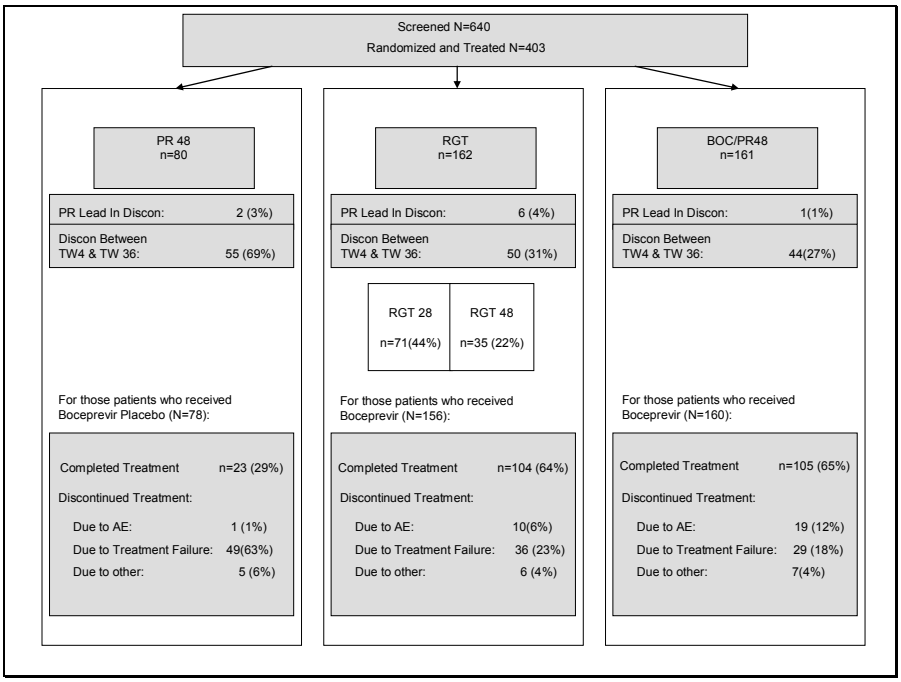
8.3 Efficacy in RESPOND-2

8.3.1 Disposition

Figure 7 displays the disposition of all screened patients in RESPOND-2. A total of 640 patients were screened, of whom 404 were randomized. Other than 1 patient, all randomized patients were treated with ≥1 dose of study medication. Nine patients

discontinued PR during the lead-in period, and never received boceprevir or placebo. Discontinuations for futility at Week 12 occurred in 49 (61%), 35 (22%), and 29 (18%) patients in the PR48, RGT, and BOC/PR48 arms, respectively.

Figure 7 Disposition of Patients in RESPOND-2



8.3.2 Patient Demographics

Demographics and baseline characteristics were similar across the three treatment arms with the exception of gender (RGT had fewer males [60%] compared with PR48 [73%] and BOC/PR48 [70%]), and region (PR48 had more patients from the Europe [36%] compared with RGT [28%] and BOC/PR48 [26%] [Table 11]. Overall, 12% of patients were black, over 88% of patients had HCV RNA levels > 800,000 IU/mL, and 19% of patients had a METAVIR fibrosis score of F3/F4. Of the 403 patients, the majority (64%) were classified as having had a relapse to previous HCV therapy.

Table 11 Baseline Demographics and Disease Characteristics, RESPOND-2

Protocol No. P05101

	Control	Experimental	
	PR48[a] n=80	RGT[a] n=162	BOC/PR48[a] n=161
Sex, n (%)			
Female	22 (28)	64 (40)	49 (30)
Male	58 (73)	98 (60)	112 (70)

Table 11 Baseline Demographics and Disease Characteristics, RESPOND-2

Protocol No. P05101

	Control	Experimental	
	PR48[a] n=80	RGT[a] n=162	BOC/PR48[a] n=161
Race, n (%)			
White	67 (84)	142 (88)	135 (84)
Black	12 (15)	18 (11)	19 (12)
Region, n (%)			
North America	51 (64)	116 (72)	119 (74)
Europe	29 (36)	46 (28)	42 (26)
Age (y)			
Mean (SD)	52.9 (8.1)	52.9 (7.4)	52.3 (7.7)
BMI			
Mean (SD)	28.2 (4.4)	28.8 (4.6)	28.3 (4.6)
Viral Load (IU/mL)			
≤400,000	6 (8)	7 (4)	7 (4)
>400,000	74 (93)	155 (96)	154 (96)
HCV Subtype (TRUGENE)[b], n(%)			
1a	38 (48)	74 (46)	77 (48)
1b	36 (45)	75 (46)	67 (42)
1 (subtype unknown)	6 (8)	13 (8)	17 (11)
METAVIR Fibrosis Score[c], n (%)			
F0/1/2	61 (76)	117 (72)	119 (74)
F3/4	15 (19)	32 (20)	31 (19)
Response to previous therapy			
Nonresponder	29 (36)	57 (35)	58 (36)
Relapser	51 (64)	105 (65)	103 (64)

8.3.3 Primary Efficacy Endpoint – Sustained Virologic Response

SVR rates were statistically significantly higher in patients receiving a boceprevir-containing regimen compared to standard of care alone: 59% RGT, 66% BOC/PR48 vs. 21% PR48 control (FAS, p<0.0001 for both comparisons) (Table 12).

The high SVR rates in patients receiving a boceprevir-containing regimen were primarily driven by higher rates of undetectable HCV RNA at the EOT compared with control. In addition, relapse rates were substantially lower in the boceprevir-containing arms (15% RGT, 12% BOC/PR48) than in the PR48 control arm (32%).

Table 12 Sustained Virologic Response in Previous Treatment Failures in the FAS Population, RESPOND-2

Protocol No. P05101

	Control	Experimental	
	PR48 n=80	RGT n=162	BOC/PR48 n=161
SVR, n (%)	17 (21.3)	95 (58.6)	107 (66.5)
Δ SVR (%)	--	37.4	45.2
95%CI for Δ	--	25.7, 49.1	33.7, 56.8
P-value	--	<0.0001	<0.0001
EOT (Undetectable HCV-RNA), n (%)	25 (31.3)	114 (70.4)	124 (77.0)
Relapse, n/N (%)	8/25 (32.0)	17/111 (15.3)	14/121 (11.6)

The small numerical difference in SVR rates between the two boceprevir-containing treatment arms appear to be due underlying differences between the two treatment arms. During the period of identical therapy (4-week PR lead-in followed by 32 weeks of boceprevir, interferon and ribavirin), more patients in the BOC/PR48 arm achieved undetectable HCV RNA than in the RGT arm. Thus, the differences in SVR (undetectable HCV RNA at follow-up week 24) may primarily reflect on-treatment differences in response while on the same treatment.

8.3.4 Sustained Virologic Response in the mITT Population

In the mITT analysis including all patients receiving ≥1 dose of boceprevir or placebo, SVR rates were significantly higher in patients receiving a boceprevir-containing regimen compared to control: 61% RGT, 67% BOC/PR48 vs. 22% PR48 control (p<0.0001 for both comparisons) (Table 13).

Table 13 Sustained Virologic Response in Previous Treatment Failures, in the mITT Population, RESPOND-2

Protocol No. P05101

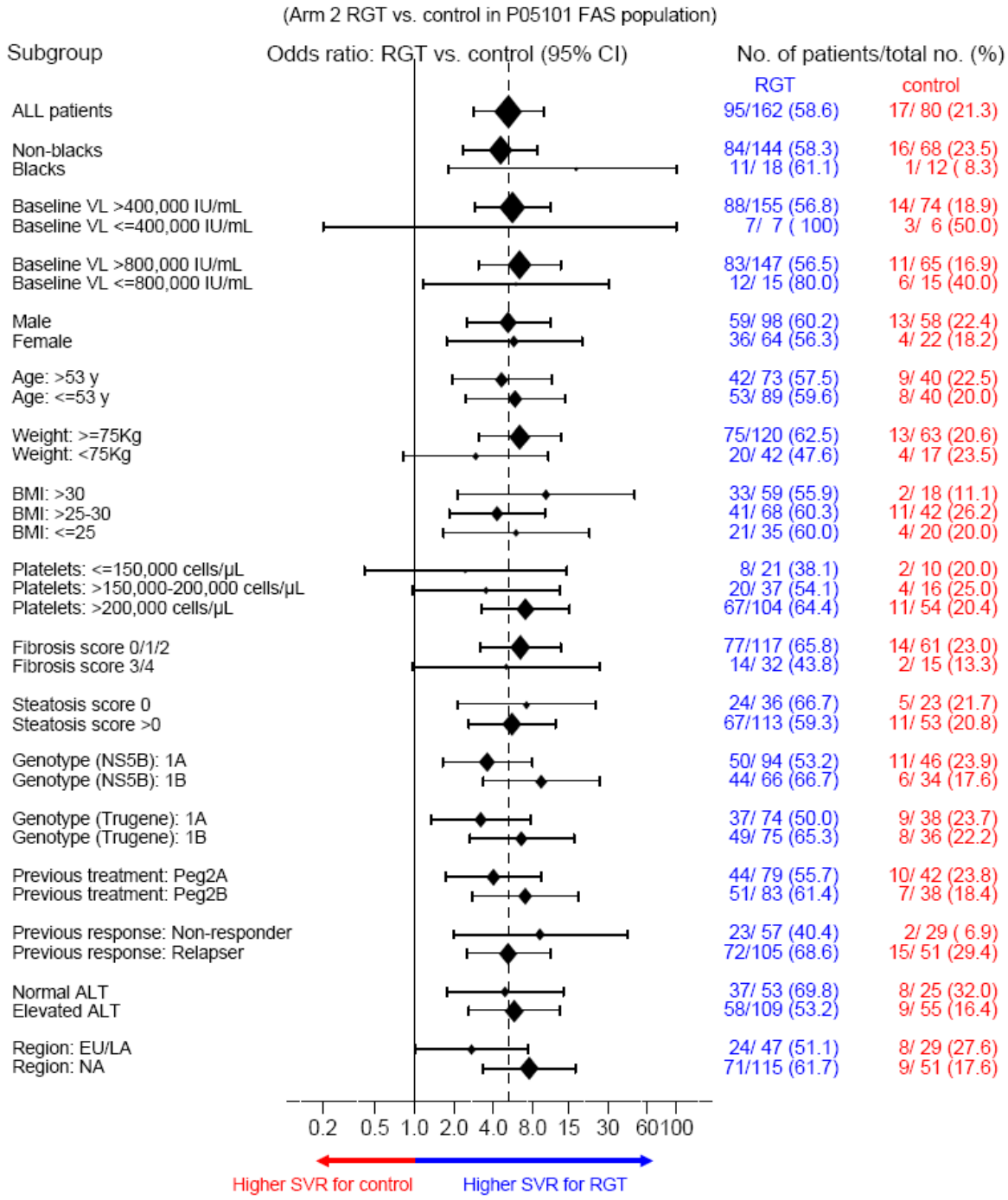
	Control	Experimental	
	PR48 n=78	RGT n=156	BOC/PR48 n=160
SVR, n (%)	17 (21.8)	95 (60.9)	107 (66.9)
Δ SVR (%)	--	39.1	45.1
95%CI for Δ	--	(27.2, 51.0)	(33.4, 56.8)
P-value	--	<0.0001	<0.0001
EOT (Undetectable HCV-RNA), n (%)	25 (32.1)	114 (73.1)	124 (77.5)
Relapse, n/N (%)	8/25 (32.0)	17/111 (15.3)	14/121 (11.6)

8.3.5 Sustained Virologic Response by Baseline Characteristics

The evaluation of treatment effect by subgroups of baseline characteristics demonstrated that the numerical odds of sustained response with boceprevir-containing regimens were larger than control across all factors (Figure 8 and Figure 9), demonstrating the robustness of the overall treatment effect, as well as consistency of treatment effect across subgroups.

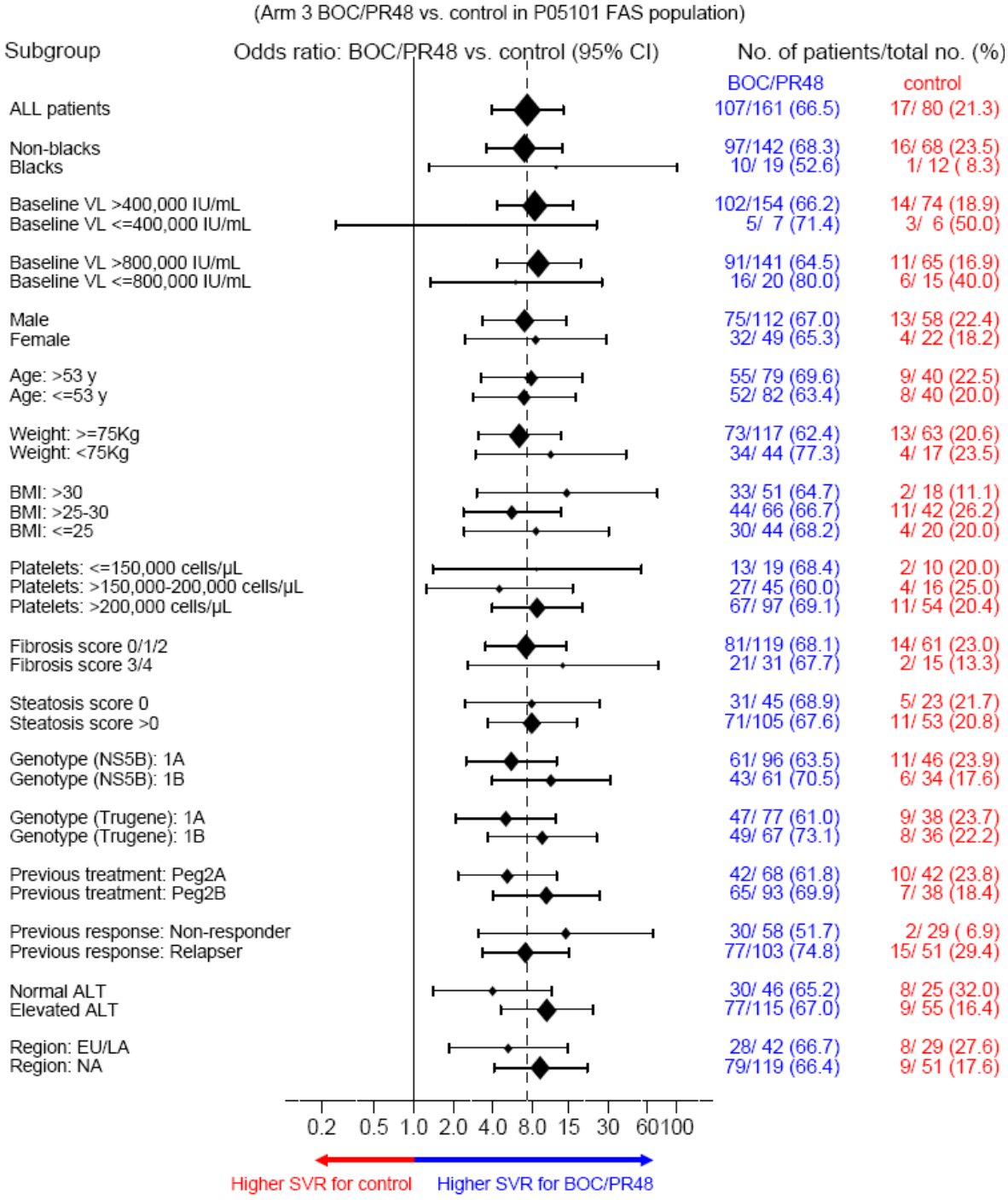
Achievement of SVR was associated with the patient's prior response to treatment at study entry. Rates of SVR for prior relapsers were 29% in the control arm vs. 69% and 75% for RGT and BOC/PR48, respectively. For prior non-responders, SVR rates were 7% in the control arm vs. 40% and 52% for RGT and BOC/PR48, respectively.

Figure 8 Odds Ratio and 95% Confidence Interval for SVR by Baseline Subgroups: RGT vs PR48 Control (FAS; RESPOND-2)



Forest plot is based on logistic regression of SVR with treatment group as covariate.

Figure 9 Odds Ratio and 95% Confidence Interval for SVR by Baseline Subgroups: BOC/PR48 vs PR48 Control (FAS; RESPOND-2)



Forest plot is based on logistic regression of SVR with treatment group as covariate.

8.3.6 Predictors of Sustained Virologic Response

Multivariable logistic regression analyses of the overall study population identified three baseline factors significantly associated with SVR (historical classification as a relapser, HCV-RNA ≤800,000 IU/mL, and the absence of advanced fibrosis) in addition to treatment allocation to a boceprevir-containing treatment regimen (Table 14).

Table 14 Multivariable Stepwise Logistic Regression for SVR by Baseline Factors, All Treatment Arms, RESPOND-2

Protocol No. P05101

Effect[a]	All Baseline Factors Included in the Model	
	Odds Ratio (95% CI)	Chi Square P-value
Treatment: BOC/PR48 vs Control	10.466 (5.200, 21.062)	<0.0001
Treatment: RGT vs Control	7.304 (3.666, 14.549)	<0.0001
Previous Treatment Response: Relapser vs NR	2.962 (1.832, 4.788)	<0.0001
Baseline HCV-RNA: ≤800,000 vs >800,000 IU/mL	2.406 (1.126, 5.140)	0.0234
Fibrosis: 0/1/2 vs 3/4	1.832 (1.046, 3.208)	0.0343

[a] Covariates included in the model consisted of treatment (BOC/PR48 vs Control, RGT vs Control), genotype (1/Other vs 1b, 1a vs 1b by NS5b, Virco), previous treatment response (relapser vs nonresponder), race (Black vs non-Black), baseline HCV-RNA (≤800,000 vs >800,000 IU/mL), sex (female vs male), age (≤40 vs >40 years), baseline weight (40-65 vs 105-125 kg, 65-80 vs 105-125 kg, 80-105 vs 105-125 kg), BMI (25-30 vs >30, 20-25 vs >30), baseline platelets (150,000-200,000 vs >200,000, ≤150,000 vs >200,000/µL), baseline fibrosis (0/1/2 vs 3/4), baseline steatosis (0 vs >0), previous treatment (PEG2a vs PEG2b), baseline ALT (elevated vs normal), statin use prior to treatment (no vs yes), and region (North America vs Europe/Latin America).

In an expanded model which included TW 4 response, interferon responsiveness (as defined by ≥1 $\log_{10}$ decline in HCV RNA level at the end of the 4-week PR lead-in) was a stronger predictor of SVR than historical response (relapser vs. non-responder) (OR=5.2, p<0.0010 and OR=2.3, p=0.0015, respectively).

8.3.7 Interferon Responsiveness at Treatment Week 4 and Sustained Virologic Response

Achievement of SVR was associated with the patient's response to peginterferon and ribavirin therapy, whether defined by their prior response to treatment at study entry (see Section 8.3.5), or by their HCV RNA level at the end of the 4-week PR lead-in (Table 15).

Table 15 Sustained Virologic Response Based on Treatment Week 4 (Lead-in) Response in Previous Treatment Failures (FAS), RESPOND-2

Protocol No. P05101

	Control	Experimental	
	PR48 n=80	RGT n=162	BOC/PR48 n=161
SVR by TW 4 Response, n/N (%)			
<1 Log Decline	0/12 (0.0)	15/46 (32.6)	15/44 (34.1)
≥1 Log Decline	17/67 (25.4)	80/110 (72.7)	90/114 (78.9)
Missing HCV-RNA	0/1 (0.0)	0/6 (0.0)	2/3 (66.7)

A total of 102 patients (28%, 27% and 15% for RGT, BOC/PR48, PR48, respectively) had a <1.0 $\log_{10}$ decline in viral load at TW 4 (after the 4-week PR lead in). SVR was achieved in none of patients in the PR48 control arm, but was achieved in 33% in the RGT arm and 34% in the BOC/PR48 arm. The findings in the control arm of RESPOND-2 are consistent with findings both in the Phase 3 treatment-naive study (SPRINT-2, Section 8.2.7) in which only 4% of patients in the PR48 control arm with a poor interferon response achieved SVR and with the findings in the IDEAL study (a 3070 patient study evaluating peginterferon alfa-2a and alfa-2b with ribavirin) in which the SVR rate was only 4% for treatment-naive patients with a "null response" (< 2 $\log_{10}$ decline in viral load at TW 12).[5] Among patients with a ≥1.0 $\log_{10}$ decline in HCV RNA at TW 4), SVR rates were 73%, 79%, and 25% in the RGT, BOC/PR48 arms, and PR48, respectively.

8.3.8 Sustained Virologic Response in Early and Late Responders: RGT compared to BOC/PR48

SVR rates in the two boceprevir treatment arms were compared to evaluate the effectiveness of boceprevir response-guided therapy (RGT) compared to fixed duration therapy (BOC/PR48) in early and late responders.

8.3.8.1 Methods

The following comparisons were conducted:

- Early Responders: SVR rates in the two boceprevir treatment arms (RGT and BOC/PR48) were compared to evaluate whether short treatment duration is as efficacious as 48-week duration among early responders.
  - This analysis included patients who completed 36-weeks of treatment and had undetectable HCV RNA levels at TW 8. Patients in RGT arm who were assigned by the IVRS to stop therapy at TW 36 (4-weeks PR lead-in followed by 32 weeks of boceprevir plus peginterferon and ribavirin) were compared to patients in the BOC/PR48 arm who were to receive 4-weeks PR lead-in followed by 44 weeks of boceprevir plus peginterferon and ribavirin.

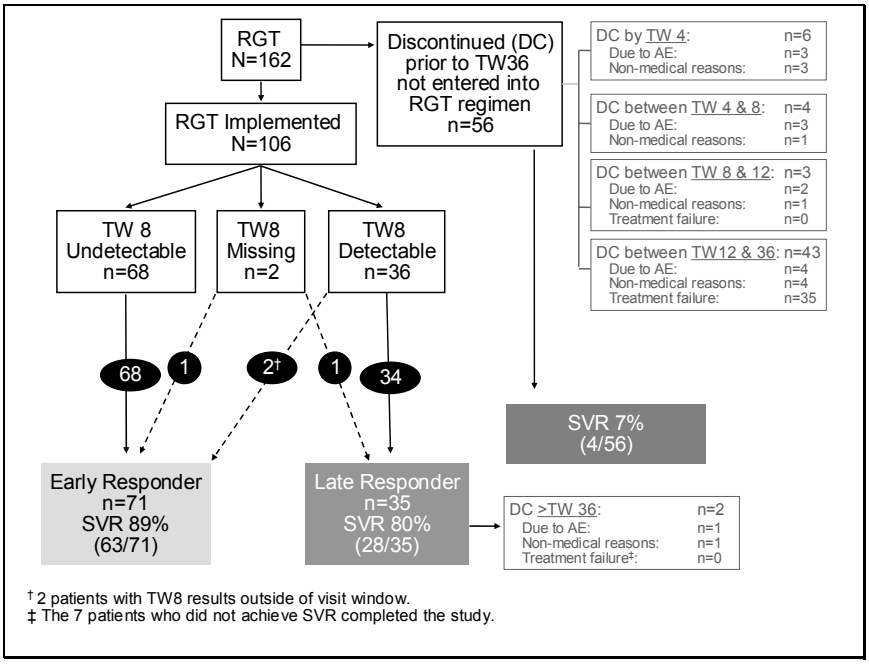
- Late responders: SVR rates in the two boceprevir treatment arms (RGT and BOC/PR48) were compared to evaluate whether a total of 48-weeks of boceprevir, peginterferon and ribavirin is needed or whether boceprevir may be stopped and peginterferon and ribavirin used alone for the last 12 weeks among late responders.
  - This analysis included patients who completed 36-weeks of treatment and had their first undetectable HCV RNA after TW 8. Patients in the RGT arm who were assigned by the IVRS to complete 48-weeks of treatment (4-weeks lead-in, followed by 32-weeks of peginterferon, ribavirin and boceprevir, followed by 12 weeks peginterferon and ribavirin alone) were compared to patients in BOC/PR48 arm who were to receive 4-weeks lead-in, followed by 44-weeks of peginterferon, ribavirin and boceprevir.

It should be noted that subgroups of early and late responders in the BOC/PR48 arm were identified solely for the purpose of the above comparisons. Patients who discontinued treatment, for any reason, prior to completing TW 36, were not included in these analyses. Therefore, as patients in both arms received identical treatment through TW 36, no bias was introduced.

8.3.8.2 Disposition

Of the 162 patients randomized to the RGT arm, 56 patients discontinued treatment prior to TW 36 and were not assigned any treatment duration by the IVRS. A schematic showing the disposition of patients in the RGT arm is presented in Figure 10.

Figure 10 Disposition of Patients in the RGT arm in RESPOND-2



8.3.8.3 Early Responders

In the RGT arm, a total of 71 patients were assigned to the shorter 36-week total treatment duration. In the BOC/PR48 arm, a total of 73 patients served as the corresponding control. Treatment with a 4-week PR lead-in followed by the addition of boceprevir for 32 weeks produced a very high SVR rate among early responders. SVR rates were 89% for patients in the RGT arm (treated with 32 weeks of boceprevir and 36 weeks total) and 97% for the corresponding patients in the fixed-duration therapy BOC/PR48 arm (treated with 44 weeks of boceprevir and 48 weeks total) (Table 16).

Table 16 Sustained Virologic Response, End of Treatment Response, and Relapse Rates in Boceprevir-containing Arms among Early Responders and Late Responders, RESPOND-2

Protocol No. P05101

	Early Responders[a]		Late Responders[a]	
	RGT	BOC/PR48	RGT	BOC/PR48
SVR, n/N (%)	63/71 (88.7)	71/73 (97.3)	28/35 (80.0)	29/40 (72.5)
EOT, n/N (%)	70/71 (98.6)	72/73 (98.6)	34/35 (97.1)	37/40 (92.5)
Relapse, n/N (%)	7/69 (10.1)	0/71 (0.0)	6/34 (17.6)	7/36 (19.4)

a Includes only patients who completed 36 weeks of treatment

8.3.8.4 Late Responders

In the RGT arm, a total of 35 patients were assigned to the 48-week total treatment duration. In the BOC/PR48 arm, a total of 40 patients were late responders and served as the corresponding control. SVR rates were 80% for patients in the RGT arm (treated with 32 weeks of boceprevir and 48 weeks total) and 73% for the corresponding patients in the fixed-duration therapy BOC/PR48 arm (treated with 44 weeks of boceprevir and 48 weeks total) (Table 16). Overall, these results provide strong support for the efficacy of the RGT regimen.

8.3.9 Sustained Virologic Response Rates Based on Treatment Week 8 HCV RNA Results: RGT compared to BOC/PR48

As discussed in Section 7.2.5, a second approach to comparing RGT and BOC/PR48 is in a patient population defined by TW 8 HCV RNA results (undetectable or detectable).

The proportion of early responders (undetectable HCV RNA at TW 8) was approximately 5.4 times higher in the boceprevir-containing arms (46% RGT, 52% BOC/PR48) compared to the PR control arm (9% PR48).

High SVR rates were seen in patients with undetectable HCV RNA at TW 8 in both the RGT and BOC/PR48 arms (86% and 88%, respectively) (Table 17). Comparable but lower SVR rates were seen in patients with detectable HCV RNA results at TW 8 in both the RGT and BOC/PR48 arms (40% and 43%, respectively). Among patients with undetectable HCV RNA at TW 8, the relapse rate was 11% (8/71) in the RGT arm compared to 7% (6/80) in the BOC/PR48 arm.

Table 17 Sustained Virologic Response Based on HCV RNA Detectability at Treatment Week 8, RESPOND-2

Protocol No. P05101

	Experimental[a]	
	RGT n=162	BOC/PR48 n=161
SVR by TW 8 Detectability, n/N (%)		
Undetectable	64/74 (86.5)	74/84 (88.1)
Detectable	29/72 (40.3)	30/70 (42.9)

a Includes only patients with HCV RNA results at TW 8

Of note, the two different analysis approaches (provided in Sections 8.3.8 and 8.3.9) show similar and high rates of SVR among early responders. In contrast, the SVR rates among late responders (Section 8.3.8) are higher than the SVR rates among patients with detectable HCV RNA at TW 8 because the latter analysis approach includes all patients with HCV RNA results at TW 8 regardless of whether they discontinued due to futility or reached TW 36.

8.3.10 Sustained Virologic Response using HCV RNA <25 IU/mL

Results consistent with the primary efficacy endpoint were obtained when SVR rates were calculated using HCV RNA <25 IU/mL as a surrogate for "undetectable HCV RNA" at follow-up timepoints (rather than the LOD of the assay [9.3 IU/mL]). SVR rates were significantly higher in patients receiving a boceprevir-containing regimen compared to control: 59% RGT, 66% BOC/PR48, and 23% PR48 control (FAS). Only two patients (one in PR48 control, one in RGT), who were considered as non-SVR in the primary efficacy analysis, were categorized as having achieved SVR using HCV RNA < 25 IU/mL.

8.4 Efficacy in Patients with Poor Interferon Responsiveness in the Pivotal Phase 3 Studies

Based on the findings from an early dose finding Phase 2 study in patients who had previously failed PR therapy (RESPOND-1; see Section 7.1.1), it had been decided to exclude patients who were previous "null responders" to peginterferon and ribavirin (as defined by a < 2.0 $\log_{10}$ decline in HCV RNA at TW 12) from the pivotal Phase 3 study in previous treatment-failure patients (RESPOND-2). The design of the Phase 3 studies, which included a 4-week PR lead-in period, allowed for a real-time

assessment of interferon responsiveness in patients. Furthermore, by noting the TW 12 response in the PR48 control group, it was possible to assess whether there were patients enrolled in the Phase 3 studies who met the "null response" criteria. This section will describe approaches to defining hard-to-treat poorly interferon responsive patients, and will demonstrate that such patients were indeed included in the boceprevir studies and demonstrated a beneficial response to boceprevir therapy.

The approach: Use of virologic response at TW 4 to define patients with poor interferon responsiveness

The following approach was undertaken to evaluate whether patients very similar to "null responders" were, in fact, included in the Phase 3 studies, and also to evaluate their outcome. The approach was as follows: (1) understand the concordance between TW 4 poor interferon responsiveness and TW 12 null response in the very large IDEAL peginterferon/ribavirin trial;[5] (2) examine the concordance of TW 4 and TW 12 definitions in the PR control arm of SPRINT-2 (it would be expected that this study in treatment-naïve patients would include "null responders") and RESPOND-2; and (3) determine whether the TW 4 definition of poor interferon responsiveness is a strong surrogate for the TW 12 definition of "null response" (by showing the very poor SVR rate in TW 4 poorly interferon responsive patients treated in the PR48 control arms).

Concordance between virologic response at TW 4 and TW 12 in the IDEAL study

The IDEAL study,[5] one of the largest CHC studies ever completed, provided strong support that patients defined as being poorly interferon responsive (HCV RNA of <1.0 $\log_{10}$ at TW 4) were largely similar to patients defined as "null responders" (HCV RNA of <2.0 $\log_{10}$ at TW 12). The correlation between TW 4 poor interferon responsiveness and TW 12 "null response" was evaluated retrospectively using data collected in IDEAL, a study of 3070 treatment-naïve patients with CHC genotype 1 infection. Patients in that study were randomized (1:1:1) to one of the following arms: peginterferon alfa-2b 1.5 µg/kg/wk or peginterferon alfa-2b 1.0 µg/kg/wk, both with weight-based dosing of ribavirin, or peginterferon alfa-2a 180 µg/wk plus ribavirin. A <2.0 $\log_{10}$ decline in HCV RNA at TW 12 was used as the futility rule for discontinuing treatment.

A total of 2098 patients had ≥2.0 $\log_{10}$ decline in HCV RNA from baseline or undetectable HCV RNA at TW 12, and 679 patients had detectable HCV RNA with <2.0 $\log_{10}$ decline from baseline at TW 12. To determine whether a <1.0 $\log_{10}$ decline in HCV RNA at TW 4 was concordant with a <2.0 $\log_{10}$ decline in HCV RNA at TW 12, a 2 x 2 table was constructed. The overall concordance for TW 4 vs. TW 12 results was 89% (2459/2777); there were 2459 patients who were in the concordant cells and only 318 patients were in discordant cells (Table 18).

Table 18 Concordance Between TW 4 and TW 12 HCV RNA Responses in the IDEAL Study

TW 4 Response	TW 12 Response	
	<2.0 $\log_{10}$ decline	≥2.0 $\log_{10}$ decline
<1.0 $\log_{10}$ decline	533	172
≥1.0 $\log_{10}$ decline	146	1926

Analysis of patients with poor interferon responsiveness in SPRINT-2

A post-hoc analysis explored the correlation between virologic response at TW 4 and TW 12 in SPRINT-2: 72/363 (20%) patients in the PR control arm met the TW 12 definition of "null response." (Based on randomization, it can be assumed that a similar proportion were likely in the boceprevir-containing arms.) The concordance between a <1.0 $\log_{10}$ decline in HCV RNA at TW 4 and a <2.0 $\log_{10}$ decline in HCV RNA at TW 12 in the PR control was high (293/329 = 89%) (Table 19).

Table 19 Concordance Between TW 4 and TW 12 Virologic Responses in the PR Control Arm, SPRINT-2

TW 4 Response	TW 12 Response	
	<2.0 $\log_{10}$ decline	≥2.0 $\log_{10}$ decline
<1.0 $\log_{10}$ decline	57	21
≥1.0 $\log_{10}$ decline	15	236

SVR rates for the patients in the PR control group who met the TW 12 definition of null response were, as expected, very low (0/72 = 0%). SVR rates for patients in the PR control group who met the TW 4 definition of poorly interferon responsive were also very low (3/78 = 4%). This was not surprising as Table 17 shows a large overlap in the patients meeting both definitions. Overall, this analysis also supports the conclusion that poor interferon responsiveness as defined at TW 4 is a strong surrogate for TW 12 null response.

Of note, in the boceprevir-containing treatment arms, patients who met the TW 4 definition of poor interferon responsiveness had ~30% higher SVR rates than similar patients in the PR control (Table 8), demonstrating the substantial benefit of boceprevir in these hard to treat patients with poor interferon responsiveness.

Analysis of patients with poor interferon responsiveness in RESPOND-2

A post-hoc analysis also explored the correlation between virologic response at TW 4 and TW 12 in RESPOND-2. Surprisingly, 15/80 patients (19%) in the PR control arm met the on-treatment TW 12 definition of "null response" – an almost identical proportion as in SPRINT-2. (Again, based on randomization, it can be assumed that a similar proportion were likely in the boceprevir-containing arms.) As with the

analysis of the IDEAL and SPRINT-2 studies, the concordance between a <1.0 log_{10} decline in HCV RNA at TW 4 and a <2.0 log_{10} decline in HCV RNA at TW 12 in the PR control was high (68/75 = 91%) (Table 20).

Table 20 Concordance Between TW 4 and TW 12 Responses in the PR Control Arm, RESPOND-2

TW 4 Response	TW 12 Response	
	<2.0 log_{10} decline	≥2.0 log_{10} decline
<1.0 log_{10} decline	10	2
≥1.0 log_{10} decline	5	58

SVR rates for the patients in the PR control group who met the TW 12 definition of null response was, as expected, very low (0/15 = 0%). SVR rates for patients in the PR control group who met the TW 4 definition of poorly interferon responsive was also very low (0/12 = 0%). This would be expected as Table 20 shows a large overlap in the patients meeting both definitions, and given the futility rule at TW 12 in RESPOND-2.

Again, it is worth noting that in the boceprevir-containing treatment arms, patients who met the TW 4 definition of poor interferon responsiveness had ~33% higher SVR rates than similar patients in the PR control (Table 15), demonstrating value of boceprevir in this subset of hard to treat patients with poor interferon responsiveness.

8.5 Efficacy of Boceprevir in Combination with Peginterferon alfa-2a and Ribavirin (P05685)

The data in this section have been submitted to the FDA, and are included in this document with the Agency's agreement. However, these data have not been reviewed by the FDA.

The pivotal Phase 3 studies demonstrated the efficacy of boceprevir when added to peginterferon alfa-2b (PegIntron®) and ribavirin. An additional Phase 3 study (P05685) was conducted in order to confirm the efficacy benefits of boceprevir when administered in combination with the other marketed pegylated interferon product, peginterferon alfa-2a (Pegasys®) and ribavirin.

Protocol P05685 was multi-center, double-blind, randomized (in a 1:2 ratio), placebo-controlled Phase 3 study in adult patients (≥18 years of age) with CHC genotype 1 infection who had failed previous PR treatment. Eligibility criteria were similar to RESPOND-2. Randomized treatment assignment was stratified based on the patient's previous response to therapy (nonresponder or relapser) and on HCV genotype (1a or 1b infection) as determined by the TRUGENE assay.

- Patients randomized to PEG2a/R received 48 weeks of peginterferon alfa-2a 1.5 µg/kg administered subcutaneously weekly (labeled dosage of Pegasys®) and oral ribavirin using weight-based dosing from 600 to 1400 mg/day divided BID, plus placebo TID starting at TW 5.

- Patients randomized to BOC/PEG2a/R received peginterferon and ribavirin for a 4-week lead-in period, followed by the addition of oral boceprevir 800 mg TID for 44 weeks.

Treatment duration in this study was the same as in the BOC/PR48 arm of RESPOND-2 in order to obtain the maximum duration of therapy for the assessment of safety. In both treatment arms, patients with detectable HCV RNA at TW 12 were discontinued for futility. These patients were considered failures in the efficacy analysis. The primary efficacy endpoint was SVR, defined as undetectable HCV RNA at follow-up week 24, in all randomized patients receiving at least one dose of study medication (FAS).

Sixty-seven patients were randomized to the PEG2a/R arm and 134 to the BOC/PEG2a/R arm. SVR rates were 21% in the PEG2a/R arm and 64% BOC/PEG2a/R arm (Table 21). SVR rates were nearly identical to the SVR rates observed in the PR48 control and BOC/PR48 arms of RESPOND-2 (21% and 66%, respectively). These study results demonstrate that the efficacy of boceprevir when added to peginterferon alfa-2a and ribavirin is similar to that when boceprevir is added to peginterferon alfa-2b; thus boceprevir markedly increases SVR rates when added to either of the currently licensed standard of care regimens.

Table 21 Sustained Virologic Response with Boceprevir Added to Peginterferon Alfa-2a Plus Ribavirin, P05685

Protocol No. P05685

	FAS		mITT	
	PEG2a/R n=67	BOC/PEG2a/R n=134	PEG2a/R n=67	BOC/PEG2a/R n=130
SVR, n (%)	14 (20.9)	86 (64.2)	14 (20.9)	86 (66.2)
Δ SVR (%)	-	43.3	-	45.3
95% CI for Δ	-	30.6, 56.0	-	32.6, 57.9
P-value	-	<0.0001	-	<0.0001
EOT (Undetectable HCV-RNA), n (%)	28 (41.8)	99 (73.9)	28 (41.8)	99 (76.2)
Relapse, n/N (%)	7/21 (33.3)	11/95 (11.6)	7/21 (33.3)	11/95 (11.6)

8.6 Long-Term Follow-Up (P05063)

P05063 is an ongoing 3.5 year long-term follow-up study enrolling patients who have received at least one dose of study medication in a previous Phase 1, 2 or 3 study of boceprevir. The objectives of the study are to confirm the durability of SVR, to characterize long-term safety, and to evaluate the natural history of CHC variants. No study therapy is administered. A total of 1064 patients were enrolled in the long-term follow-up study as of the data cut-off date for the 3-month safety update report (23 NOV 2010); 17% of all enrolled subjects had completed follow-up, 9% discontinued, and 73% of patietns were ongoing at the time of the data cutoff date. The median duration of participation in this ongoing trial is 2 years. None of the sustained virologic responders enrolled in this study have had HCV RNA virology results that met the study criteria for relapse, underscoring the durability of response. There were no late occurring SAEs related to study drug.

8.7 Guidelines for Dosing and Administration of Boceprevir

Guidelines for dosing and administration of a boceprevir have been developed based on the efficacy results demonstrated in the pivotal Phase 3 trials in treatment-naïve patients and in patients who previously failed PR therapy. The proposed administration of boceprevir uses a response-guided-therapy algorithm.

Patients who are previously untreated:

- Initiate therapy with peginterferon alpha and ribavirin for 4 weeks (TW 1 through TW 4).
- Add boceprevir 800 mg three times daily to the peginterferon alpha and ribavirin regimen at TW 5. Based on the patient's HCV-RNA levels at TW 8 and TW 24, use the following RGT guidelines to determine duration of treatment (Table 22).

Table 22 Duration of Therapy Using Response-Guided Therapy (RGT) in Patients Who are Previously Untreated

ASSESSMENT (HCV-RNA Results)		**ACTION**
At TW 8	**At TW 24**	
Undetectable	Undetectable	Complete three-drug regimen at TW 28.
Detectable	Undetectable	1. Continue all three medications until TW 28; and then 2. Administer peginterferon alpha and ribavirin until TW 48.
Any Result	Detectable	Discontinue three-drug regimen.

Patients who have failed previous PR therapy:

- Initiate therapy with peginterferon alpha and ribavirin for 4 weeks (TW 1 through TW 4).

- Add boceprevir 800 mg three times daily to the peginterferon alpha and ribavirin regimen at TW 5. Based on the patient's HCV-RNA levels at TW 8 and TW 12, use the following RGT guidelines to determine duration of treatment (Table 23).

Table 23 Duration of Therapy Using Response-Guided Therapy (RGT) in Patients Who Have Failed Previous Therapy

ASSESSMENT (HCV-RNA Results)		**ACTION**
At TW 8	**At TW 12**	
Undetectable	Undetectable	Continue three-drug regimen until completion through TW 36.
Detectable	Undetectable	1. Continue all three medications until TW 36; and then 2. Administer peginterferon alpha and ribavirin until TW 48.
Any Result	Detectable	Discontinue three-drug regimen.

8.8 Efficacy Conclusions

- The addition of boceprevir to peginterferon and ribavirin leads to high rates of sustained virologic response in patients who are treatment-naïve and in patients who have failed prior peginterferon and ribavirin treatment.
- Using a response guided-therapy algorithm, patients with early virologic response (undetectable HCV RNA at TW 8) can effectively be treated with shorter durations of therapy (28 weeks for treatment naïve patients; 36 weeks for patients who had previously failed PR therapy).
- There were no sub-groups of patients for whom standard of care was more efficacious than therapy with boceprevir added to peginterferon and ribavirin.
- High response rates were observed in subgroups that are usually poor responders to peginterferon and ribavirin, e.g., blacks and patients with poor interferon responsiveness (as defined by a < 1 $\log_{10}$ reduction in HCV RNA levels at treatment week 4).

9.0 RESISTANCE

Resistance analysis focused on 10 positions (“loci”) in the amino acid sequence of the NS3/4A protease domain at which substitutions (“variants”) were verified (by *in vitro* testing) to confer reduced susceptibility to boceprevir (See Section 4.0). The amino acids found at the 10 loci of NS3 in the reference genotype 1a strain H77 used in the analysis were V36, Q41, F43, T54, V55, R155, A156, V158, I170, and L175. The amino acids found at the 10 loci of NS3 in the reference genotype 1b strain Con1 used in the analysis of samples with genotype 1b were V36, Q41, F43, T54, V55, R155, A156, V158, V170, and M175. Samples with genotype designated

1a1b, genotype 1 (subtype not specified) and non-1 genotypes were analyzed using genotype 1a H77 as reference.

Variants with amino acid substitutions that conferred reduced susceptibility to boceprevir *in vitro* or that were detected at higher frequency in postbaseline samples from patients receiving boceprevir were termed resistance-associated amino acid variants (RAVs).

In the pivotal Phase 3 studies, plasma samples were evaluated at baseline by population sequencing to detect amino acid variants in the NS3/4A protease known or suspected to be associated with reduced susceptibility to boceprevir. Among patients who failed to achieve SVR, the emergence of boceprevir RAVs was monitored by isolating plasma viral RNA, determining the amino acid sequences encoded by the NS3/4A protease gene via population sequencing, and comparing the sequence with the sequence at baseline for the same patient.

9.1 Detection of Resistance-Associated Variants at Baseline

Baseline sequence data were available for 980 of 1020 (96%) patients treated with boceprevir in the pivotal Phase 3 studies. Of these, 66/980 (7%) patients had viruses with RAVs detected at baseline. In patients with genotype 1a virus with RAVs detected, the most common baseline RAVs were V36L, V55A, V55I and T54S. In patients with genotype 1b virus with RAVs detected, the most common baseline RAVs was T54S.

Similar results were observed in patients in the PR48 control arms of the pivotal Phase 3 studies. Among patients with baseline sequence data, 27/419 (6%) patients had viruses with RAVs detected at baseline. In patients with genotype 1a virus, the most common baseline RAV detected was V55A. In subjects with genotype 1b virus, the most common baseline RAVs detected were T54S and V170M.

9.2 Detection of Resistance-Associated Variants Postbaseline

The emergence of RAVs was evaluated in a pooled analysis of patients treated with boceprevir in SPRINT-2 and RESPOND-2. The most frequently detected post-baseline RAVs in viruses from these patients were amino acid substitutions V36M or R155K in genotype 1a viruses or T54A, T54S, A156S or V170A in genotype 1b viruses.

Among boceprevir-treated non-SVR patients with samples sequenced; the emergence of postbaseline RAVs was detected in 155/295 (53%). Most non-SVR patients with viruses harboring postbaseline RAVs were poorly interferon responsive (74%; 115/155). The detection of postbaseline RAVs was highly associated with viral breakthrough (detectable HCV RNA after being undetectable) or incomplete virologic response (initial decrease in HCV RNA followed by ≥ 1 $\log_{10}$ increase from nadir); viruses isolated from 75% (18/24) of viral breakthrough patients and 92% (54/59) of

incomplete virologic response patients displayed viruses with RAVs. RAVs were detected in viruses isolated from 41% (32/78) of relapsers.

RAVs were detected with similar frequencies in RGT and BOC/PR treatment arms. In the RGT arms, viruses isolated from 52% (82/158) of patients with postbaseline samples sequenced had viruses with detectable RAVs compared to 52% (74/142) of viruses isolated from patients in the 48-week BOC/PR arms.

9.3 Resistance-Associated Variants at Baseline and SVR

An exploratory analysis comparing the frequency and distribution of RAVs detected in boceprevir-treated patients at baseline with the frequency and distribution of post-baseline RAVs detected in non-SVR boceprevir-treated patients indicated that some RAVs at baseline (V36M, R155K, T54A/S and/or V55A) may be associated with treatment failure in poorly interferon responsive patients.

Of the 66 boceprevir-treated patients with RAVs detected at baseline, 43 had V36M, R155K, T54A/S, and/or V55A (RAVs frequently detected in non-SVR patients postbaseline, see Section 9.2) and 23 had V36I/L, Q41H, V55I, V170M and/or M175L (RAVs not frequently detected in non-SVR patients postbaseline). Of the 43 patients who had V36M, R155K, T54A/S, and/or V55A, 36 were interferon responsive and 7 were poorly interferon responsive (as defined at TW 4, see Section 7.2.4). The SVR rate among interferon responsive patients with V36M, R155K, T54A/S, and/or V55A RAVs at baseline (78%; 28/36) was similar to the SVR rate among interferon responsive patients with V36I/L, Q41H, V55I, V170M and/or M175L at baseline (73%; 11/15). In contrast, the SVR rate among poorly interferon responsive patients with V36M, R155K, T54A/S, and/or V55A RAVs at baseline was 0% (0/7), compared to SVR rates of 50% (3/6) among poorly interferon responsive patients with baseline RAVs V36I/L, Q41H, V55I, V170M and/or M175L. Although the numbers of patients are small, the combination of poor interferon responsiveness and V36M, R155K, T54A/S, and/or V55A RAVs at baseline appears to correspond with a poor treatment outcome. The numbers of patients with a combination of poor interferon responsiveness and baseline V36M, R155K, T54A/S, and/or V55A RAVs represented 1% (7/1020) of patients treated with boceprevir.

9.4 Decline in Postbaseline Resistance Associated Variants in Long-Term Follow-up

Patients enrolled in the long-term follow-up study (P05063) and who had viruses with postbaseline RAVs detectable at the end of their participation in a boceprevir Phase 1, 2 or 3 clinical study had plasma samples monitored every 3 to 6 months to assess for RAVs by population sequencing. A total of 183 patients had sufficient follow-up data to be included in a 2-year interim analysis of the data. (Note: All of these patients had been enrolled in a Phase 2 clinical study.)

The rate of loss of detection of RAVs by population sequencing was calculated in the Kaplan-Meier analysis for the four most common RAVs and for all RAVs (including

the most common RAVs) and is shown for patients infected with genotype 1a or 1b virus in Table 24. (Note: These results are from long term follow-up of patients enrolled in Phase 2; the analysis for patients enrolled in the pivotal Phase 3 studies is ongoing.) The loss of detection of RAVs by population sequencing varies depending on the RAV and likely reflects the relative fitness of the specific RAVs.

Table 24 Loss of Detection of RAVs by Population Sequencing in Boceprevir-Treated Patients

Protocol No. P05063

Parameter	V36M	T54A	T54S	R155K	All
Number of Patients with RAVs detected at the start of long-term follow-up	97	22	102	119	183
Number of Patients with detectable RAVs remaining at the end of 2 years follow-up	11	0	37	36	78
Percent of Patients with detectable RAVs remaining at the end of 2 years follow-up	11.3 %	0 %	36.3 %	30.3%	42.6%
Median time detectable RAV remain in years (95% CI)	0.78 (0.50, 1.01)	0.24 (0.10, 0.47)	1.43 (1.06, 1.58)	1.28 (1.07, 1.46)	1.50 (1.35, 1.75)

CI = confidence interval; RAV = resistance-associated variant

9.5 Resistance Conclusions

- Boceprevir resistance-associated variants (RAVs) were detected in a small proportion of patients prior to treatment.
- Among all patients treated with boceprevir, as a result of the high SVR rates, the emergence of RAVs was infrequent. However, RAVs were detected in the majority of patients with virologic breakthrough and incomplete virologic response.
- Interferon responsiveness plays a role in the emergence of RAVs on boceprevir treatment.
- After stopping therapy in patients who did not achieve SVR and whose viruses developed RAVs, the number of RAVs declined over time. Different RAVs declined at different rates likely reflecting differing effects on viral fitness.

10.0 SAFETY

The designs of the Phase 2 and Phase 3 treatment-naïve studies (SPRINT-1 and SPRINT-2, respectively) and the Phase 3 study in previous PR treatment failures (RESPOND-2) permitted an integrated analyses of the general safety of boceprevir (800 mg TID) in combination with peginterferon alfa-2b and weight-based ribavirin

therapy and a comparison with the safety of peginterferon and ribavirin standard of care. In all 3 studies, boceprevir was to be administered for 24 weeks or more. (Note: The Phase 2 dose finding study in treatment-failure patients [RESPOND-1] was not included in the integrated safety analysis because none of the patients received boceprevir 800 mg TID in combination with peginterferon and ribavirin from the beginning of the study, and none received more than 24 weeks of boceprevir 800 mg TID with peginterferon and ribavirin.)

For the integrated safety assessment, these studies were pooled by combining data in all arms including boceprevir therapy (BOC/PR) and then combining data from the standard of care (PR) arms. Unless otherwise noted, all safety tables include patients who received at least one dose of any study medication (i.e., the full analysis set in the SPRINT-1, SPRINT-2, and RESPOND-2 studies).

Treatment-related, treatment-emergent adverse events (AEs) include all events that occurred on or after the treatment start date up to 30 days after the treatment stop date and were considered, by the investigator, to be “possibly related” or “probably related” to study drug administration. The investigator reported relatedness of an AE to the regimen, not to a specific study drug. Serious adverse events (SAEs) and deaths include all events that occurred after enrollment or within 30 of study completion.

10.1 Extent of Drug Exposure

A total of 1548 patients in the BOC/PR arms and 547 patients in the PR arms of the key studies received at least one dose of any study medication (BOC/PR total excludes 36 PR subjects in SPRINT-1 who were allowed to crossover to BOC/PR because of treatment failure). Of the 1548 patients, 1212 patients received at least 20 weeks and 607 received at least 44 weeks of boceprevir in combination with PR. The total exposure to boceprevir was 839.7 person years. Actual treatment durations, including any PR lead-in treatment, ranged from one to 362 days (median exposure 201 days in the BOC/PR arms). In previous treatment-failure patients, exposure to PR control was substantially less than exposure to BOC/PR (median treatment duration 104 vs 253 days, respectively) which should be carefully considered when comparing safety between the treatment arms. In treatment-naïve patients, treatment exposure was nearly equal (median treatment duration 216 days in PR control arm vs 197 days in BOC/PR arm). This difference between study populations may be explained by the earlier futility rule in previous treatment failures (TW 12) compared with treatment-naïve patients (TW 24). The inclusion of 28-week treatment arms in SPRINT-1 and RGT arms in SPRINT-2 and RESPOND-2 accounts for the decrease in the number of patients on BOC/PR after TW 28 in the treatment-naïve population, and TW 36 in the treatment-failure population (Table 25)

Table 25 Distribution of Treatment Duration in the Key Studies: Interval From Beginning to End of Treatment

Protocol Nos. P03523, P05216, and P05101

Treatment Duration	Number (%) of Patients					
	Treatment Naïve SPRINT-1/ SPRINT-2		PEG/R Treatment Failure RESPOND-2		All Patients	
	PR n=467	BOC/PR n=1225	PR n=80	BOC/PR n=323	PR n=547	BOC/PR n=1548
Received Any Treatment	467 (100)	1225 (100)	80 (100)	323 (100)	547 (100)	1548 (100)
TW 4	449 (96)	1189 (97)	79 (99)	318 (98)	528 (97)	1507 (97)
TW 8	441 (94)	1140 (93)	77 (96)	312 (97)	518 (95)	1452 (94)
TW 12	433 (93)	1108 (90)	75 (94)	307 (95)	508 (93)	1415 (91)
TW 24	399 (85)	974 (80)	25 (31)	238 (74)	424 (78)	1212 (78)
TW 28	306 (66)	897 (73)	23 (29)	231 (72)	329 (60)	1128 (73)
TW 36	227 (49)	498 (41)	23 (29)	224 (69)	250 (46)	722 (47)
TW 48	214 (46)	467 (38)	23 (29)	140 (43)	237 (43)	607 (39)
Statistics (Days)						
Mean	240.2	226.1	166.1	244.7	229.4	230
Median	216	197	104	253	198	201

10.2 Overview of Safety

The proportions of subjects reporting treatment-related, treatment emergent adverse events (AEs), serious adverse events (SAEs), life-threatening AEs, and study drug discontinuations due to adverse events (AEs) were similar in the PR control and BOC/PR arms (Table 26). Dose modifications were primarily due to anemia in both groups (see Section 10.4). In most patients, dose modifications were made for peginterferon and/or ribavirin.

Table 26 Overview of Adverse Events, Deaths, and Study Drug Discontinuation and Dose Modifications Due to Adverse Events in the Key Studies

Protocol Nos. P03523, P05216, and P05101

	Number (%) of Patients					
	Treatment-naïve SPRINT-1/ SPRINT-2		PEG/R Treatment Failure RESPOND-2		All Patients	
	PR[a] n=467	BOC/PR n=1225	PR n=80	BOC/PR n=323	PR n=547	BOC/PR n=1548
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Treatment-Emergent AE	460 (99)	1217 (99)	77 (96)	321 (99)	537 (98)	1538 (99)
Treatment-Related Treatment-Emergent AE	456 (98)	1212 (99)	77 (96)	320 (99)	533 (97)	1532 (99)
Serious AE	39 (8)	125 (10)	4 (5)	39 (12)	43 (8)	164 (11)
Death[b]	4 (1)	3 (<1)	0	1 (<1)	4 (1)	4 (<1)
Life-Threatening	7 (1)	13 (1)	0	9 (3)	7 (1)	22 (1)
Study Drug Discontinuation Due to AE	65 (14)	172 (14)	2 (3)	33 (10)	67 (12)	205 (13)
Dose Modification Due to AE[c]	121 (26)	505 (41)	11 (14)	100 (31)	132 (24)	605 (39)

Note: Patients may have had more than one AE.

a. Excludes events for 36 patients in SPRINT-1 after they crossed over from PR to BOC/PR.

b. Deaths are included in serious AE count.

c. Excludes patients who discontinued due to AEs.

10.3 Treatment-Related, Treatment-Emergent Adverse Events

The most commonly reported treatment-related, treatment-emergent AEs (≥10% incidence) in the key studies are summarized in Table 27. Fatigue, anemia, nausea, headache, and dysgeusia were reported in >35% of patients. Anemia and dysgeusia (change in the sense of taste) are the only two events that were reported with a ≥10% difference in the combined BOC/PR arms compared with combined PR control arms.

Table 27 Treatment-Related, Treatment-Emergent Adverse Events in the Key Studies (Incidence Greater Than or Equal to 10% in Any Treatment Arm)

Protocol Nos. P03523, P05216, and P05101

	Treatment-naive SPRINT-1/ SPRINT-2		PEG/R Treatment Failure RESPOND-2		All Patients	
	PR[a] n=467	BOC/PR n=1225	PR n=80	BOC/PR n=323	PR[a] n=547	BOC/PR n=1548
Median Treatment Duration (Days)	216	197	104	253	198	201
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects Reporting Any Adverse Event	456 (98)	1212 (99)	77 (96)	320 (99)	533 (97)	1532 (99)
Blood and Lymphatic System Disorders	200 (43)	721 (59)	19 (24)	157 (49)	219 (40)	878 (57)
Anaemia	142 (30)	611 (50)	16 (20)	144 (45)	158 (29)	755 (49)
Neutropenia	88 (19)	304 (25)	8 (10)	46 (14)	96 (18)	350 (23)
Cardiac Disorders	20 (4)	37 (3)	1 (1)	8 (2)	21 (4)	45 (3)
Congenital, Familial and Genetic Disorders	1 (<1)	0	0	2 (1)	1 (<1)	2 (<1)
Ear and Labyrinth Disorders	28 (6)	65 (5)	3 (4)	18 (6)	31 (6)	83 (5)
Endocrine Disorders	30 (6)	45 (4)	0	8 (2)	30 (5)	53 (3)
Eye Disorders	70 (15)	221 (18)	5 (6)	38 (12)	75 (14)	259 (17)
Gastrointestinal Disorders	320 (69)	979 (80)	47 (59)	253 (78)	367 (67)	1232 (80)
Diarrhoea	88 (19)	279 (23)	12 (15)	74 (23)	100 (18)	353 (23)
Dry Mouth	44 (9)	128 (10)	7 (9)	46 (14)	51 (9)	174 (11)
Dysgeusia	73 (16)	427 (35)	9 (11)	141 (44)	82 (15)	568 (37)
Nausea	187 (40)	556 (45)	30 (38)	134 (41)	217 (40)	690 (45)
Vomiting	54 (12)	228 (19)	6 (8)	43 (13)	60 (11)	271 (18)

Table 27 Treatment-Related, Treatment-Emergent Adverse Events in the Key Studies (Incidence Greater Than or Equal to 10% in Any Treatment Arm)

Protocol Nos. P03523, P05216, and P05101

	Treatment-naive SPRINT-1/ SPRINT-2		PEG/R Treatment Failure RESPOND-2		All Patients	
	PR[a] n=467	BOC/PR n=1225	PR n=80	BOC/PR n=323	PR[a] n=547	BOC/PR n=1548
General Disorders and Administration Site Conditions	434 (93)	1122 (92)	68 (85)	292 (90)	502 (92)	1414 (91)
Asthenia	84 (18)	179 (15)	13 (16)	68 (21)	97 (18)	247 (16)
Chills	137 (29)	410 (33)	24 (30)	105 (33)	161 (29)	515 (33)
Fatigue	272 (58)	710 (58)	40 (50)	179 (55)	312 (57)	889 (57)
Influenza Like Illness	115 (25)	264 (22)	20 (25)	75 (23)	135 (25)	339 (22)
Injection Site Erythema	59 (13)	131 (11)	7 (9)	36 (11)	66 (12)	167 (11)
Injection Site Reaction	52 (11)	141 (12)	5 (6)	25 (8)	57 (10)	166 (11)
Irritability	108 (23)	266 (22)	10 (13)	67 (21)	118 (22)	333 (22)
Pain	39 (8)	124 (10)	3 (4)	24 (7)	42 (8)	148 (10)
Pyrexia	151 (32)	394 (32)	17 (21)	91 (28)	168 (31)	485 (31)
Hepatobiliary Disorders	5 (1)	12 (1)	1 (1)	0	6 (1)	12 (1)
Immune System Disorders	2 (<1)	2 (<1)	0	0	2 (<1)	2 (<1)
Infections and Infestations	82 (18)	233 (19)	11 (14)	47 (15)	93 (17)	280 (18)
Injury, Poisoning and Procedural Complications	9 (2)	30 (2)	0	6 (2)	9 (2)	36 (2)
Investigations	83 (18)	235 (19)	10 (13)	60 (19)	93 (17)	295 (19)
Weight Decreased	55 (12)	134 (11)	7 (9)	36 (11)	62 (11)	170 (11)
Metabolism and Nutrition Disorders	129 (28)	373 (30)	16 (20)	98 (30)	145 (27)	471 (30)
Decreased Appetite	112 (24)	304 (25)	13 (16)	82 (25)	125 (23)	386 (25)
Musculoskeletal and Connective Tissue Disorders	201 (43)	527 (43)	32 (40)	142 (44)	233 (43)	669 (43)
Arthralgia	79 (17)	216 (18)	11 (14)	66 (20)	90 (16)	282 (18)
Myalgia	110 (24)	275 (22)	19 (24)	79 (24)	129 (24)	354 (23)
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	1 (<1)	2 (<1)	0	1 (<1)	1 (<1)	3 (<1)

Table 27 Treatment-Related, Treatment-Emergent Adverse Events in the Key Studies (Incidence Greater Than or Equal to 10% in Any Treatment Arm)

Protocol Nos. P03523, P05216, and P05101

	Treatment-naive SPRINT-1/ SPRINT-2		PEG/R Treatment Failure RESPOND-2		All Patients	
	PR[a] n=467	BOC/PR n=1225	PR n=80	BOC/PR n=323	PR[a] n=547	BOC/PR n=1548
Nervous System Disorders	271 (58)	753 (61)	44 (55)	180 (56)	315 (58)	933 (60)
Dizziness	67 (14)	219 (18)	8 (10)	50 (15)	75 (14)	269 (17)
Headache	196 (42)	554 (45)	38 (48)	129 (40)	234 (43)	683 (44)
Psychiatric Disorders	267 (57)	679 (55)	33 (41)	160 (50)	300 (55)	839 (54)
Anxiety	55 (12)	151 (12)	5 (6)	39 (12)	60 (11)	190 (12)
Depression	96 (21)	255 (21)	12 (15)	47 (15)	108 (20)	302 (20)
Insomnia	154 (33)	403 (33)	16 (20)	95 (29)	170 (31)	498 (32)
Renal and Urinary Disorders	15 (3)	43 (4)	3 (4)	8 (2)	18 (3)	51 (3)
Reproductive System and Breast Disorders	22 (5)	46 (4)	0	9 (3)	22 (4)	55 (4)
Respiratory, Thoracic and Mediastinal Disorders	180 (39)	532 (43)	29 (36)	163 (50)	209 (38)	695 (45)
Cough	88 (19)	194 (16)	12 (15)	63 (20)	100 (18)	257 (17)
Dyspnoea	73 (16)	227 (19)	13 (16)	69 (21)	86 (16)	296 (19)
Dyspnoea Exertional	36 (8)	100 (8)	4 (5)	36 (11)	40 (7)	136 (9)
Skin and Subcutaneous Tissue Disorders	307 (66)	807 (66)	34 (43)	198 (61)	341 (62)	1005 (65)
Alopecia	126 (27)	333 (27)	13 (16)	71 (22)	139 (25)	404 (26)
Dry Skin	82 (18)	214 (17)	6 (8)	70 (22)	88 (16)	284 (18)
Pruritus	111 (24)	265 (22)	14 (18)	61 (19)	125 (23)	326 (21)
Rash	87 (19)	200 (16)	4 (5)	49 (15)	91 (17)	249 (16)
Social Circumstances	1 (<1)	2 (<1)	0	2 (1)	1 (<1)	4 (<1)
Surgical and Medical Procedures	1 (<1)	2 (<1)	0	0	1 (<1)	2 (<1)
Vascular Disorders	20 (4)	62 (5)	2 (3)	17 (5)	22 (4)	79 (5)

Note: Note: Incidences provided for all System Organ Classes. Preferred Terms provided only for treatment-related treatment-emergent AEs with incidence ≥10% in any treatment arm. Patients may have had more than one AE.

a. Excludes events for 36 patients in SPRINT-1 after they crossed over from PR to BOC/PR.

10.4 Deaths, Serious Adverse Experiences, and Adverse Events Associated with Discontinuation of Study Drug

Deaths: Of the 2095 treated patients, 8 died during the course of the key studies (Table 26). Four deaths (4/1548, <1%) occurred in the BOC/PR arms and 4 deaths (4/547, 1%) occurred in the PR control arms. Of the AEs that resulted in death, 6 were considered by the investigators to be unlikely related to study drugs and two were possibly related to study drug (one suicide each in the PR and BOC/PR arms, respectively).

Serious Adverse Events: SAEs were reported in 11% of patients in the BOC/PR arms and 8% of patients in the PR control arms (Table 28). Most of the SAEs were reported in only one patient; SAEs reported in more than one patient were reported with somewhat higher frequency in BOC/PR than PR control: hematologic 19/1548 (1%) vs 2/547 (<1%); gastrointestinal 29/1548 (2%) vs 6/547 (1%); and psychiatric 24/1548 (2%) vs 5/547 (1%), respectively.

Table 28 Serious Adverse Events in the Key Studies (Incidence Greater Than or Equal to 1% in Any Treatment Arm)

Protocol Nos. P03523, P05216, and P05101

	Number (%) of Patients									
	Treatment-naive SPRINT-1/SPRINT-2				PEG/R Treatment Failure RESPOND-2				All Patients			
	PR[a] n=467		BOC/PR n=1225		PR n=80		BOC/PR n=323		PR[a] n=547		BOC/PR n=1548	
Median Treatment Duration (Days)	216		197		104		253		198		201	
Subjects Reporting Any SAE	39	(8)	125	(10)	4	(5)	39	(12)	43	(8)	164	(11)
System Organ Class Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	(%)	(%)	n	(%)
Blood and Lymphatic System Disorders	2	(<1)	14	(1)	0		5	(2)	2	(<1)	19	(1)
Anaemia	1	(<1)	9	(1)	0		5	(2)	1	(<1)	14	(1)
Neutropenia	0		7	(1)	0		0		0		7	(<1)
Cardiac Disorders	2	(<1)	9	(1)	0		4	(1)	2	(<1)	13	(1)
Ear and Labyrinth Disorders	0		2	(<1)	0		0		0		2	(<1)
Endocrine Disorders	1	(<1)	0		0		0		1	(<1)	0	
Eye Disorders	1	(<1)	6	(<1)	0		0		1	(<1)	6	(<1)
Gastrointestinal Disorders	6	(1)	20	(2)	0		9	(3)	6	(1)	29	(2)
Abdominal Pain	1	(<1)	3	(<1)	0		2	(1)	1	(<1)	5	(<1)
General Disorders and Administration Site Conditions	4	(1)	19	(2)	1	(1)	5	(2)	5	(1)	24	(2)
Chest Pain	0		6	(<1)	1	(1)	3	(1)	1	(<1)	9	(1)

Table 28 Serious Adverse Events in the Key Studies (Incidence Greater Than or Equal to 1% in Any Treatment Arm)

Protocol Nos. P03523, P05216, and P05101

	Number (%) of Patients											
	Treatment-naive SPRINT-1/SPRINT-2				PEG/R Treatment Failure RESPOND-2				All Patients			
	PR[a] n=467		BOC/PR n=1225		PR n=80		BOC/PR n=323		PR[a] n=547		BOC/PR n=1548	
Hepatobiliary Disorders	3	(1)	1	(<1)	1	(1)	1	(<1)	4	(1)	2	(<1)
Cholelithiasis	2	(<1)	0		1	(1)	0		3	(1)	0	
Infections and Infestations	8	(2)	30	(2)	1	(1)	6	(2)	9	(2)	36	(2)
Appendicitis	1	(<1)	0		0		3	(1)	1	(<1)	3	(<1)
Gastroenteritis	0		5	(<1)	1	(1)	0		1	(<1)	5	(<1)
Injury, Poisoning and Procedural Complications	4	(1)	9	(1)	0		2	(1)	4	(1)	11	(1)
Investigations	1	(<1)	2	(<1)	0		0		1	(<1)	2	(<1)
Metabolism and Nutrition Disorders	0		5	(<1)	0		3	(1)	0		8	(1)
Musculoskeletal and Connective Tissue Disorders	1	(<1)	5	(<1)	0		3	(1)	1	(<1)	8	(1)
Intervertebral Disc Protrusion	0		2	(<1)	0		2	(1)	0		4	(<1)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	6	(1)	8	(1)	0		1	(<1)	6	(1)	9	(1)
Nervous System Disorders	3	(1)	13	(1)	1	(1)	3	(1)	4	(1)	16	(1)
Parkinsonism	0		0		1	(1)	0		1	(<1)	0	
Psychiatric Disorders	5	(1)	16	(1)	0		8	(2)	5	(1)	24	(2)
Depression	1	(<1)	4	(<1)	0		4	(1)	1	(<1)	8	(1)
Homicidal Ideation	0		2	(<1)	0		2	(1)	0		4	(<1)
Suicidal Ideation	2	(<1)	7	(1)	0		5	(2)	2	(<1)	12	(1)
Renal and Urinary Disorders	1	(<1)	0		0		0		1	(<1)	0	
Reproductive System and Breast Disorders	0		1	(<1)	0		0		0		1	(<1)
Respiratory, Thoracic and Mediastinal Disorders	1	(<1)	8	(1)	0		3	(1)	1	(<1)	11	(1)
Dyspnea	0		2	(<1)	0		2	(1)	0		4	(<1)
Skin and Subcutaneous Disorders	0		2	(<1)	0		0		0		2	(<1)
Social Circumstances	1	(<1)	1	(<1)	0		0		1	(<1)	1	(<1)

Table 28 Serious Adverse Events in the Key Studies (Incidence Greater Than or Equal to 1% in Any Treatment Arm)

Protocol Nos. P03523, P05216, and P05101

	Number (%) of Patients					
	Treatment-naive SPRINT-1/SPRINT-2		PEG/R Treatment Failure RESPOND-2		All Patients	
	PR[a] n=467	BOC/PR n=1225	PR n=80	BOC/PR n=323	PR[a] n=547	BOC/PR n=1548
Surgical and Medical Procedures	2 (<1)	1 (<1)	0	1 (<1)	2 (<1)	2 (<1)

Note: Incidences provided for all System Organ Classes. Preferred Terms provided only for SAEs with incidence ≥1% in any treatment arm. Patients may have had more than one SAE.

Study Drug Discontinuation Because of Adverse Events: There was no difference in study drug discontinuations for AEs between the BOC/PR (13%) and PR control (12%) arms (Table 29). Events resulting in discontinuation were similar to those seen in previous studies with peginterferon and ribavirin and included anemia, asthenia, fatigue, nausea, depression, and suicidal ideation.

Table 29 All Adverse Events That Led to Study Drug Discontinuation in the Key Studies (Incidence Greater Than or Equal to 1% in Any Treatment Arm)

Protocol Nos. P03523, P05216, and P05101

	Treatment Naïve SPRINT-1/ SPRINT-2		PEG/R Treatment Failure RESPOND-2		All Patients	
	PR[a] n=467	BOC/PR n=1225	PR n=80	BOC/PR n=323	PR[a] n=547	BOC/PR n=1548
Median Treatment Duration (Days)	216	197	104	253	198	201
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects Reporting Any Adverse Event	65 (14)	172 (14)	2 (3)	33 (10)	67 (12)	205 (13)
Blood and Lymphatic System Disorders	5 (1)	26 (2)	0	5 (2)	5 (1)	31 (2)
Anaemia	4 (1)	18 (1)	0	5 (2)	4 (1)	23 (1)
Neutropenia	0	11 (1)	0	0	0	11 (1)
Cardiac Disorders	3 (1)	3 (<1)	0	1 (<1)	3 (1)	4 (<1)
Ear and Labyrinth Disorders	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)

Table 29 All Adverse Events That Led to Study Drug Discontinuation in the Key Studies (Incidence Greater Than or Equal to 1% in Any Treatment Arm)

Protocol Nos. P03523, P05216, and P05101

	Treatment Naïve SPRINT-1/ SPRINT-2		PEG/R Treatment Failure RESPOND-2		All Patients	
	PR[a] n=467	BOC/PR n=1225	PR n=80	BOC/PR n=323	PR[a] n=547	BOC/PR n=1548
Endocrine Disorders	1 (<1)	2 (<1)	0	0	1 (<1)	2 (<1)
Eye Disorders	2 (<1)	11 (1)	0	0	2 (<1)	11 (1)
Gastrointestinal Disorders	8 (2)	26 (2)	0	7 (2)	8 (1)	33 (2)
Oesophageal Pain	2 (<1)	11 (1)	0	3 (1)	2 (<1)	14 (1)
Vomiting	0	8 (1)	0	1 (<1)	0	9 (1)
General Disorders and Administration Site Conditions	22 (5)	53 (4)	0	10 (3)	22 (4)	63 (4)
Asthenia	4 (1)	6 (<1)	0	3 (1)	4 (1)	9 (1)
Chills	3 (1)	1 (<1)	0	0	3 (1)	1 (<1)
Fatigue	14 (3)	29 (2)	0	3 (1)	14 (3)	32 (2)
Influenza Like Illness	3 (1)	2 (<1)	0	1 (<1)	3 (1)	3 (<1)
Irritability	1 (<1)	9 (1)	0	2 (1)	1 (<1)	11 (1)
Hepatobiliary Disorder	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Immune System Disorders	0	1 (<1)	0	0	0	1 (<1)
Infections and Infestations	2 (<1)	7 (1)	0	0	2 (<1)	7 (<1)
Injury, Poisoning and Procedural Complications	1 (<1)	2 (<1)	0	0	1 (<1)	2 (<1)
Investigations	5 (1)	6 (<1)	0	1 (<1)	5 (1)	7 (<1)
Metabolism and Nutrition Disorders	1 (<1)	3 (<1)	0	2 (1)	1 (<1)	5 (<1)
Decreased Appetite	1 (<1)	1 (<1)	0	2 (1)	1 (<1)	3 (<1)
Musculoskeletal and Connective Tissue Disorders	3 (1)	5 (<1)	0	0	3 (1)	5 (<1)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	2 (<1)	1 (<1)	0	0	2 (<1)	1 (<1)
Nervous System Disorders	9 (2)	22 (2)	2 (3)	4 (1)	11 (2)	26 (2)
Disturbance in Attention	0	1 (<1)	0	2 (1)	0	3 (<1)
Headache	6 (1)	6 (<1)	0	0	6 (1)	6 (<1)
Pregnancy, Puerperium and Perinatal Conditions	0	1 (<1)	0	0	0	1 (<1)

Table 29 All Adverse Events That Led to Study Drug Discontinuation in the Key Studies (Incidence Greater Than or Equal to 1% in Any Treatment Arm)

Protocol Nos. P03523, P05216, and P05101

	Treatment Naïve SPRINT-1/ SPRINT-2		PEG/R Treatment Failure RESPOND-2		All Patients	
	PR[a] n=467	BOC/PR n=1225	PR n=80	BOC/PR n=323	PR[a] n=547	BOC/PR n=1548
Psychiatric Disorders	18 (4)	32 (3)	0	9 (3)	18 (3)	41 (3)
Anxiety	4 (1)	5 (<1)	0	1 (<1)	4 (1)	6 (<1)
Depression	4 (1)	14 (1)	0	3 (1)	4 (1)	17 (1)
Homicidal Ideation	0	2 (<1)	0	2 (1)	0	4 (<1)
Suicidal Ideation	2 (<1)	7 (1)	0	3 (1)	2 (<1)	10 (1)
Renal and Urinary Disorders	1 (<1)	0	0	0	1 (<1)	0
Respiratory, Thoracic and Mediastinal Disorders	4 (1)	8 (1)	0	2 (1)	4 (1)	10 (1)
Dyspnoea	4 (1)	2 (<1)	0	2 (1)	4 (1)	4 (<1)
Skin and Subcutaneous Tissue Disorders	4 (1)	13 (1)	0	0	4 (1)	13 (1)
Social Circumstances	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Vascular Discorders	1 (<1)	4 (<1)	0	0	1 (<1)	4 (<1)

Note: Incidences provided for all System Organ Classes. Preferred Terms provided only for AEs that led to study drug discontinuation with incidence ≥1% in any treatment arm. Patients may have had more than one AE.

a: Excludes events for 36 patients in SPRINT-1 after they crossed over from PR to BOC/PR.

Dose Modification Because of Adverse Events: AEs led to dose modifications (of any of the study medications) in 39% of patients in the BOC/PR arms and in 24% of subjects in the PR control arms of the key studies (Table 26). Most dose modifications occurred in the context of management of anemia (24% BOC/PR vs 12% PR) and neutropenia (12% BOC/PR vs 7% PR). In most patients, dose modifications were made for peginterferon and ribavirin. Only 1% of patients had modifications solely of boceprevir or placebo due to AEs. Due to the increased incidence of anemia, the boceprevir-containing arms had a greater proportion of patients with ribavirin dose reduction (29%) than did the PR control arm (16%).

10.5 Adverse Events

10.5.1 Effect on Hematopoietic Cell Lines

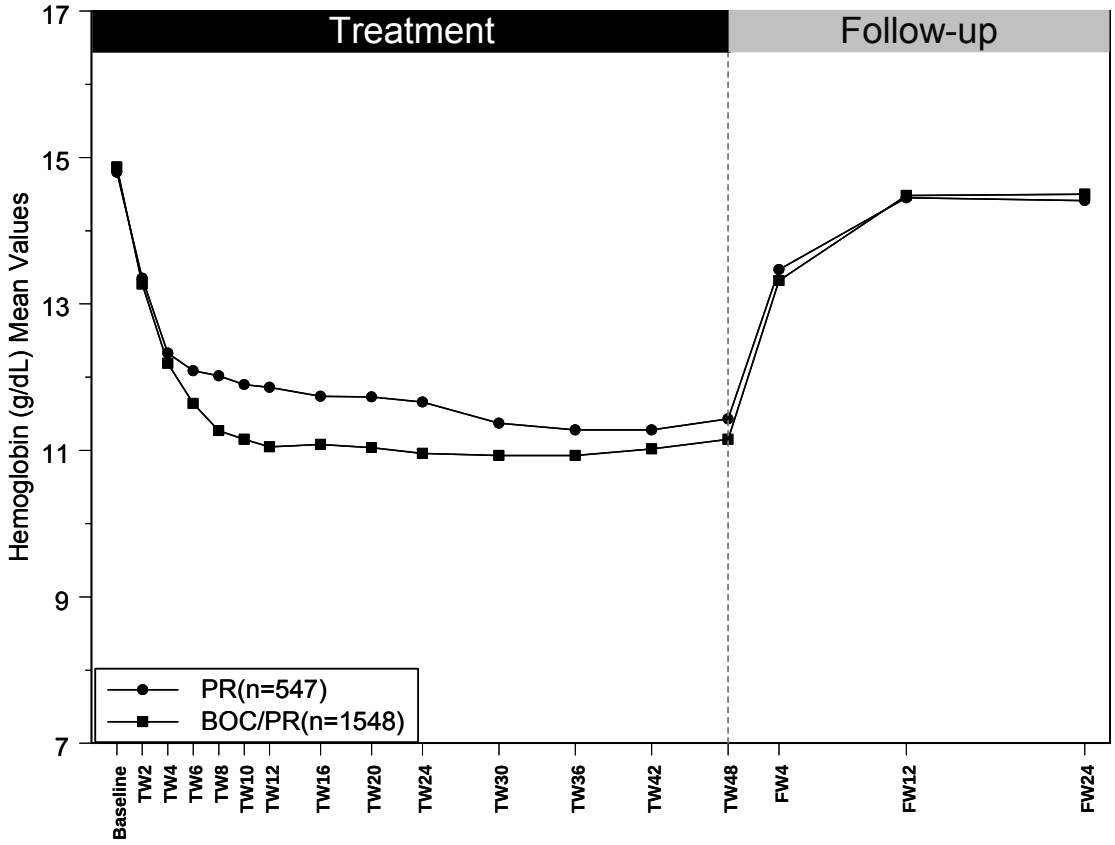
PR therapy causes decreases in red blood cell, neutrophil, and platelet counts, in that order of descending magnitude and clinical importance. Anemia is primarily the result of hemolysis secondary to ribavirin combined with bone marrow suppressive effects of interferon. Neutropenia is primary a result of the bone marrow suppressive effects of interferon.

Boceprevir has an incremental effect on hematopoiesis beyond that seen with PR therapy which led to increase rates of anemia, and to a lesser extent neutropenia, compared to PR control.

10.5.1.1 Anemia

Boceprevir administered as monotherapy did not cause anemia, nor was there any effect of boceprevir on RBC survival, production, or destruction, or on markers of anemia (see Section 6.1). When boceprevir was added to PR, an incremental decrease in hemoglobin concentration of approximately 1 g/dL beyond that seen with PR was observed during treatment in the key studies. This incremental decrease was reached about 4 weeks after the start of boceprevir treatment (at TW 8) (Figure 11). As previously described with PR, hemoglobin concentrations returned to baseline within approximately 12 weeks after study drug discontinuation.

Figure 11 Mean Hemoglobin (g/dL) Over Time in the Key Studies



Patients receiving boceprevir were more likely to develop WHO Grade 3 (3% vs 1% control) and Grade 4 (<1% vs 0 control) decreases in hemoglobin concentration (Table 30) and to meet protocol-specified guidelines for dose reduction (hemoglobin 8.5 to <10 g/dL; 42% BOC/PR vs 26% PR) and study drug discontinuation (hemoglobin <8.5 g/dL; 7% BOC/PR vs 3% PR).

Treatment with BOC/PR, female sex, low baseline hemoglobin, and age greater than 40 years were identified as risk factors for the development of anemia (defined as hemoglobin <10 g/dL) for both the treatment-naïve and previous treatment-failure populations, with the additional risk factor of black race in the previous treatment failures.

Consistent with the described effect on hemoglobin levels, the proportion of patients with anemia reported as an AE was higher in the BOC/PR arms (49%) than in the PR control arms (29%) (Table 27). Symptoms of fatigue, dizziness, dyspnea, and exertional dyspnea were more common in anemic patients (hemoglobin <10 g/dL).

Table 30 Distribution of Lowest Hemoglobin Values, by Modified WHO Grade, During Treatment in the Key Studies

Protocol Nos. P03523, P05216, and P05101

Hemoglobin (g/dL)	WHO Grade	Number (%) of Patients					
		Treatment Naïve SPRINT-1/ SPRINT-2		PEG/R Treatment Failure RESPOND-2		All Patients	
		PR[a] n=467	BOC/PR n=1225	PR n=80	BOC/PR n=323	PR[a] n=547	BOC/PR n=1548
Number of Subjects Included[b]		n=461	n=1215	n=80	n=322	n=541	n=1537
≥11.0	0	207 (45)	295 (24)	44 (55)	82 (25)	251 (46)	377 (25)
9.5 to <11.0	1	177 (38)	551 (45)	26 (33)	139 (43)	203 (38)	690 (45)
8.0 to <9.5	2	71 (15)	342 (28)	9 (11)	83 (26)	80 (15)	425 (28)
6.5 to <8.0	3	6 (1)	24 (2)	1 (1)	17 (5)	7 (1)	41 (3)
<6.5	4	0	3 (<1)	0	1 (<1)	0	4 (<1)

Note: The table summarizes the worst category observed within the period per patient per laboratory test (ie, the nadir for the hematologic parameters). Only patients with at least one treatment value for a given laboratory test are included.

a: Excludes laboratory values for 36 patients in SPRINT-1 after they crossed over from PR to BOC/PR.

b: Only patients with at least one treatment value for a given laboratory test are included.

Management of Anemia

Ribavirin dose reduction and/or erythropoietin use are the standard tools for the management of anemia associated with PR therapy. The protocols for the key studies provided guidelines for the use of erythropoietin (consistent with the guidelines recommended by the FDA for hepatitis Phase 2 and Phase 3 clinical studies) and/or ribavirin dose reduction, but anemia management decisions (including the decision whether to use erythropoietin) were at the discretion of the investigator. Erythropoietin was provided by the sponsor at no cost to the patient (which may have increased the use of erythropoietin in the management of anemia

in these clinical studies). The use of erythropoietin and/or ribavirin dose reduction was recommended if the hemoglobin concentration decreased to <10 g/dL; it was recommended that ribavirin be interrupted or discontinued if the hemoglobin concentration decreased to <8.5 g/dL (Table 31). Treatment interruptions were not to exceed two consecutive weeks in duration.

Table 31 Guidelines Used in Clinical Studies for Use of Erythropoietin for Patients with Anemia

Hemoglobin Value	Management	Monitoring
≤10 g/dL	Initiate erythropoietin 40,000 units SC, weekly (long acting formulations of erythropoietin MUST be avoided).	After initiation of erythropoietin therapy, weekly monitoring of hemoglobin values is recommended.
>10 to <12 g/dL	If receiving erythropoietin, reduce the dose of erythropoietin by 25% to 50% if hemoglobin levels increase by >1g/dL within 2 weeks or >2 g/dL within 4 weeks.	If hemoglobin is stable on 4 consecutive weekly measures while on a stable dosing regimen of erythropoietin, then decrease the monitoring of hemoglobin to every 2 weeks, and then if stable to every 2 to 4 weeks.
≥12 g/dL	Hold the next erythropoietin dose with subsequent tapering of the dose to maintain target range (10-12 g/dL).	Continue to monitor at every 4 weeks of therapy, or more frequently if clinically indicated.

Anemia was managed by ribavirin dose reduction alone in 7% and 10% of BOC/PR and PR control patients, respectively; with erythropoietin use alone in 33% and 37% of patients, respectively, and with both ribavirin dose reduction and erythropoietin use in 46% and 32% of patients, respectively. Thirty-nine (3%) patients in the BOC/PR arms and 2 (<1%) patients in the PR control arms received a transfusion. (Blood transfusion decisions were at the discretion of the investigator; no criteria were provided in the study protocols.)

Association of Anemia with Higher SVR Rates

In genotype 1 CHC patients, SVR rates have been reported to be higher in anemic patients compared with nonanemic patients, independent of erythropoietin use.[15] It has been hypothesized that hemoglobin decline is a pharmacodynamic marker of ribavirin exposure. Across all boceprevir and control arms in both study populations, anemia was consistently associated with higher rates of SVR. For the RGT, BOC/PR48, and PR48 control arms in SPRINT-2, rates of SVR were 69%, 76% and 56% among patients with a nadir hemoglobin level less than 10 g/dL during the treatment period, compared with 60%, 56% and 31% among patients with a hemoglobin level of 10 g/dL or greater during the treatment period. For the RGT, BOC/PR48, and PR48 control arms in RESPOND-2, rates of SVR were 76%,76% and 25% among patients with a nadir hemoglobin level less than 10 g/dL during the treatment period, compared with 57%, 43% and 20% among patients with a hemoglobin level of 10 g/dL or greater during the treatment period.

In an exploratory analysis, the high SVR rates seen in patients with anemia were independent of the intervention used for the management of anemia (ribavirin dose reduction and/or erythropoietin). (Note: The pivotal Phase 3 studies were not designed to assess the effect of different anemia strategies on SVR.) Among BOC/PR patients (pooled RGT and BOC/PR48 treatment arms) with a nadir hemoglobin level less than 10 g/dL in SPRINT-2, rates of SVR were 78%, 74%, 71%, in patients whose anemia was managed with ribavirin dose reduction alone, erythropoietin alone, or ribavirin dose reduction and erythropoietin, respectively. Among BOC/PR patients (pooled RGT and BOC/PR48 treatment arms) with a nadir hemoglobin level less than 10 g/dL in RESPOND-2, rates of SVR were 83%, 80%, and 72% in patients whose anemia was managed with ribavirin dose reduction alone, erythropoietin alone, or ribavirin dose reduction and erythropoietin, respectively.

Safety with Erythropoietin Use

The potential risks of erythropoietin have been well described in other disease states for which it is indicated. Erythropoietin use has been associated with cardiovascular, thromboembolic and oncologic events in these patient populations. Hypertension is among the most commonly reported AE.

Erythropoietin appeared to be tolerated by patients in the key studies. Cardiac, vascular, and thromboembolic events occurred only sporadically and no more frequently in patients who used erythropoietin than in those who did not. Baseline and the highest post-baseline blood pressure values were similar in patients who received erythropoietin compared to those who did not. Neither group experienced significant blood pressure changes post-baseline. Use of erythropoietin was not associated with an increased incidence of oncologic events (total study period 72 weeks). Medically important AEs potentially attributable to erythropoietin were rare and generally occurred with similar frequency in patients who received erythropoietin and those who did not. No patient who died had used erythropoietin.

A serious adverse event of pure red cell aplasia (PRCA) was reported in a 56 year-old white female in Spain in the BOC/PR arm (SPRINT-2) who received erythropoietin. The patient had been treated with erythropoietin starting at TW 6 for the management of anemia (hemoglobin 9.6 g/dL). At TW 38, while still receiving erythropoietin, the patient had a hemoglobin 6.0 g/dL, reticulocyte count 0.002%, neutrophil count of 0.54 x 10^9/L, and platelet count of 38 x 10^9/L. All study medications were discontinued, and the patient's neutropenia and thrombocytopenia resolved, but anemia (transfusion dependent) persisted. Anti-erythropoietin antibodies were reported as positive, and bone marrow biopsy showed no RBC precursors. An evaluation for acute parvovirus infection was not performed. Pure red cell aplasia in association with neutralizing antibodies to native erythropoietin has been previously reported in association with the use of recombinant erythropoietin growth factors in patients with chronic renal failure and in patients receiving interferon-based therapy and ribavirin.

10.5.1.2 Neutropenia

After treatment initiation in the key studies, there was a rapid decline and then a plateau in the mean neutrophil counts after 8 weeks to 12 weeks that was maintained to the end of treatment, with counts returning to baseline levels at the end of follow-up. The pattern seen was typical for interferon-based therapies.

Patients receiving boceprevir were more likely to develop WHO Grade 3 (22% vs 13% control) and Grade 4 (7% vs 4% control) neutrophil counts and to meet protocol-specified guidelines for dose reduction (neutrophil count $<0.75 \times 10^9$/L) (17% vs 29% control) and study drug discontinuation (neutrophil count $<0.5 \times 10^9$/L) (7% vs 4% control) (Table 32). Patients with lower baseline neutrophil counts were more likely to meet the guidelines for dose modification or study drug discontinuation.

Table 32 Lowest Neutrophil Counts During Treatment, by Modified WHO Category, in the Key Studies

Protocol No. P03523, P05216, and P05101

Neutrophils (10^9/L)	WHO Grade	Number (%) of Patients					
		Treatment-naive SPRINT-1/ SPRINT-2		PEG/R Treatment Failure RESPOND-2		All Patients	
		PR[a] n=467	BOC/PR n=1225	PR n=80	BOC/PR n=323	PR[a] n=547	BOC/PR n=1548
Number of Subjects Included[b]		n=461	N=1215	n=80	n=322	n=541	n=1537
>1.5	0	110 (24)	178 (15)	24 (30)	47 (15)	134 (25)	225 (15)
1.0 to 1.5	1	152 (33)	348 (29)	31 (39)	105 (33)	183 (34)	453 (29)
0.75 to <1.0	2	115 (25)	316 (26)	15 (19)	87 (27)	130 (24)	403 (26)
0.5 to <0.75	3	65 (14)	279 (23)	7 (9)	62 (19)	72 (13)	341 (22)
<0.5	4	19 (4)	94 (8)	3 (4)	21 (7)	22 (4)	115 (7)

Note: The table summarizes the worst category observed within the period per subject per laboratory test (ie, the nadir for the hematologic parameters). Only patients with at least one treatment value for a given laboratory test are included.

[a] Excludes laboratory values for 36 patients in SPRINT-1 after they crossed over from PR to BOC/PR.

[b] Only patients with at least one treatment value for a given laboratory test are included.

Treatment-related, treatment-emergent AEs of neutropenia were reported by 23% of all patients in the BOC/PR arms and 18% in the PR arms of the key studies. The incidence of treatment-related, treatment-emergent AEs in the System Organ Class (SOC) of Infections and Infestations was similar in the BOC/PR (18%) and PR control (17%) arms; the incidence of treatment-emergent AEs in this SOC was also similar (34% BOC/PR, 34% PR control). Likewise, the distribution of severity of treatment-related, treatment-emergent infection/infestations was similar, with severe infections/infestations reported in less than 1% of BOC/PR and PR control patients.

There were 3 severe cases of neutropenia associated with severe infections in patients receiving BOC/PR in the key studies: epiglottitis, upper respiratory tract infection requiring treatment with 3 antibiotics including vancomycin, and salmonella gastroenteritis. In addition, 2 cases of life-threatening neutropenia/decreased neutrophil count were reported (without a specific infection), both in patients receiving BOC/PR. One patient developed multi-organ system failure due to sepsis, and the other experienced a fever of 104.5°F.

10.5.1.3 Thrombocytopenia

Mean platelet counts decreased from baseline during treatment, reaching a plateau from TW 12 to TW 48. After the discontinuation of study medications, platelet counts returned to near baseline by the end of follow-up.

Treatment-related, treatment-emergent thrombocytopenia was reported in 4% of patients in the BOC/PR arms and 1% of patients in the PR control arms. Patients receiving boceprevir were more likely to develop WHO Grade 3 (3% vs 1% control) and Grade 4 (<1% vs 0 control) decreases in platelet counts and to meet protocol-specified guidelines for dose reduction (platelet count $<50 \times 10^9$/L) (3% vs 1% control) and study drug discontinuation (platelet count $<25 \times 10^9$/L) (<1% vs 0 control) (Table 33). Patients with lower baseline platelet counts were more likely to meet the criteria for dose modification or study drug discontinuation.

Table 33 Lowest Platelet Counts During Treatment, by Modified WHO Category, in the Key Studies

Protocol No. P03523, P05216, and P05101

Platelets (10^9/L)	WHO Grade	Number (%) of Patients					
		Treatment-naive SPRINT-1/ SPRINT-2		PEG/R Treatment Failure RESPOND-2		All Patients	
		PR[a] n=467	BOC/PR n=1225	PR n=80	BOC/PR n=323	PR[a] n=547	BOC/PR n=1548
Number of Subjects Included[b]		n=458	n=1214	n=80	n=332	n=538	n=1536
>100	0	397 (87)	833 (69)	66 (83)	206 (64)	463 (86)	1039 (68)
70 to 100	1	47 (10)	252 (21)	12 (15)	73 (23)	59 (11)	325 (21)
50 to <70	2	9 (2)	91 (7)	2 (3)	31 (10)	11 (2)	122 (8)
25 to <50	3	5 (1)	35 (3)	0	12 (4)	5 (1)	47 (3)
<25	4	0	3 (<1)	0	0	0	3 (<1)

Note: The table summarizes the worst category observed within the period per subject per laboratory test (ie, the nadir for the hematologic parameters).

[a] Excludes laboratory values for 36 patients in SPRINT-1 after they crossed over from PR to BOC/PR.

[b] Only patients with at least one treatment value for a given laboratory test are included.

There was only one case of significant bleeding (hematemesis) during follow-up week 4 in a patient with Grade 3 thrombocytopenia and a history of pre-existing portal hypertension and portal gastropathy. None of the three patients with Grade 4 thrombocytopenia experienced significant bleeding, although all three experienced epistaxis which, in each case, was considered mild and did not require intervention.

10.5.2 Dysgeusia

Treatment-related, treatment-emergent dysgeusia occurred more frequently in patients in the BOC/PR arms, but was rarely treatment limiting. Verbatim terms coded to the adverse event dysgeusia included metallic taste in mouth, earthy after taste and bitter taste. Dysgeusia was reported in 37% of boceprevir-treated patients, and was sometimes associated with gastrointestinal symptoms such as nausea, vomiting diarrhea and weight loss. Most events of dysgeusia were mild in severity; less than 1% reported dose modification or discontinued therapy due to dysgeusia. There were no SAEs of dysgeusia.

10.5.3 Rash and Skin Eruption Adverse Events

Rash, primarily related to ribavirin use, is relatively common with PR standard of care.

Treatment-related, treatment-emergent rash/skin eruption adverse events were reported in 30% of patients in the BOC/PR arms and 27% of patients in the PR control arms. In RESPOND-2, patients receiving boceprevir were more likely to develop rash compared with PR control. Differences in exposure to therapy may account for some of this difference. It is also of note that reports of rash were unusually low in the PR control arm of this study (compared to historical data).

Most rash events were mild or moderate in severity. Severe rash/skin eruption was reported for 6 patients in the PR control group (6/547, 1%) and 6 patients in the BOC/PR group (6/1548, <1%). In these 12 patients, severe rash led to discontinuation of study medication in only 1 patient (rash maculopapular, BOC/PR), and dose reduction or interruption of study medication in 4 patients (1 BOC/PR, 3 PR control). Two patients were treated with oral steroids (one with generalized rash [PR control] and the other with erythematous rash [BOC/PR, also considered an SAE]), 8 patients were treated with topical medications and/or oral antihistamines (5 BOC/PR, 3 PR control), and 2 patients (BOC/PR) were not treated with medication.

One rash/skin eruption SAE was reported in the key studies; erythematous rash, was reported in a patient in the BOC/PR48 arm of SPRINT-2. The event did not require dose modification or hospitalization and the patient was treated with oral steroids. The event resolved while the patient continued to receive study drugs. There were no reports of Stevens-Johnson syndrome or toxic epidermal necrolysis.

10.6 Safety in RGT and BOC/PR48 Arms (SPRINT-2)

In the pivotal Phase 3 studies, RGT allowed early responders to receive shorter durations of treatment (total treatment duration of 28-weeks for treatment-naïve, 36-weeks for treatment-failure populations) compared to 48-week fixed-duration therapy (BOC/PR48). Theoretically, shorter durations of therapy should translate into a safety benefit, and indeed the advantages of shorter therapy duration are apparent in an analysis of safety in the RGT and BOC/PR48 arms of SPRINT-2.

It would not be expected that the incidence of AEs that have an early onset should differ in a comparison of RGT to BOC/PR48 wks; rather differences might be expected in AEs that have a late onset and also in the duration of AEs. Among patients with undetectable HCV RNA at TW 8 in SPRINT-2, SAEs were reported by similar proportions of patients in the RGT and BOC/PR48 arms (10% and 11%, respectively). The proportion of patients who discontinued study drug due to AEs was less in the RGT arm (9%) compared with the BOC/PR48 arm (17%). The proportion of patients with hemoglobin values < 8 g/dL was lower in the RGT vs BOC/PR48 arms (2% vs 8%). The mean duration of erythropoietin use was reduced by 46% among patients in the RGT arm compared with patients in the BOC/PR48 arm. Among patients reporting moderate/severe depression, the mean duration of symptoms was shorter in the RGT arm compared to the BOC/PR arm (15 weeks vs 28 weeks).

10.7 Safety in Special Populations: Intrinsic Factors and Comorbid Conditions

Safety in special populations was assessed in the integrated safety database.

Intrinsic Factors

The safety profile of boceprevir was generally similar in patients subgroups based on sex, race, age, and body mass index.

Female sex and age greater than 40 years were identified as risk factors for the development of anemia for both the treatment-naïve and treatment-failure populations, with the additional risk factor of black race in the treatment-failure population. The incidence of moderate anemia (Hgb of 8 to < 9.5 g/dL) was greater in females than in males in both the BOC/PR and PR treatment arms; however, the difference in the proportion of patients with moderate anemia between females and males in the BOC/PR arm was greater than the difference between sexes in the PR control arm. The incidence of severe anemia (Hgb < 8g/dL) was similar when comparing females to males. Among the small group of elderly patients (≥65 years of age), anemia was reported as an adverse event in 31/38 (82%) compared to 55% in patients 55-64 years of age.

Comorbid Conditions

The safety profile of boceprevir was generally similar in patient subgroups based on the common comorbid conditions: cirrhosis, hypertension, diabetes mellitus, psychiatric disorders, and a history of drug abuse.

Among patients with cirrhosis (n=143), the addition of boceprevir to peginterferon and ribavirin was generally well tolerated. Anemia and thrombocytopenia were more common in patients with cirrhosis receiving BOC/PR vs. those without cirrhosis. These AEs were also more common in cirrhotic patients receiving PR than non-cirrhotic patients; boceprevir did not appear to exacerbate this difference. The anemia in cirrhotics was managed with somewhat more erythropoietin use (42% vs 38%) and transfusions (4% vs 2%) than in patients without cirrhosis.

Hypertensive patients who received BOC/PR were more likely to experience exertional dyspnea than non-hypertensive patients. The safety profile of boceprevir was similar in patients with and without diabetes mellitus, psychiatric disorders, and drug abuse. There was no evidence that boceprevir exacerbated psychiatric AEs in patients with a history of psychiatric disorders or drug abuse.

10.8 Safety of Boceprevir in Combination with Peginterferon alfa-2a and Ribavirin (P05685)

The data in this section have been submitted to the FDA, and are included in this document with the Agency's agreement. However, these data have not been reviewed by the FDA.

In this study comparing treatment with 48-weeks of peginterferon alfa-2a and ribavirin (PEG2a/R) with peginterferon alfa-2a and ribavirin for a 4-week lead-in period, followed by the addition of boceprevir for 44 weeks (BOC/PEG2a/R), treatment-emergent AEs occurred in 100% of patients in both treatment arms. SAEs were reported in 13% (18/134) of patients in the BOC/PEG2a/R arm and 10% (7/67) of patients in the PEG2a/R treatment arm. There were 2 deaths in the study (both in the BOC/PEG2a/R arm), one of which occurred 2 days post-treatment (heart failure) and the other 15 days post-treatment (staphylococcus aureus bronchopneumonia).

Anemia was reported in 50% (67/134) patients in the BOC/PEG2a/R arm and 33% (22/67) of patients in the PEG2a/R arm. There were no SAEs related to anemia. One patient (BOC/PEG2a/R arm) discontinued due to anemia. Erythropoietin was administered to 47% (63/134) of boceprevir recipients (BOC/PEG2a/R) and 30% (20/67) of controls (PEG2a/R). Neutropenia was reported for 31% (42/134) in the BOC/PEG2a/R arm and 18% (12/67) patients in the PEG2a/R arm. Grade 4 neutropenia (neutrophil count $<0.5 \times 10^9$/L) was reported for 14% (19/134) in the BOC/PEG2a/R arm and 3% (2/67) patients in the PEG2a/R arm. There were 2 SAEs related to neutropenia in the BOC/PEG2a/R arm; these 2 patients discontinued treatment due to neutropenia. Dysgeusia was a frequent adverse event, reported

more than twice as often in patients receiving boceprevir than control (39% BOC/PEG2a/R vs. 15% PEG2a/R).

10.9 Safety Conclusions

- The safety profile of boceprevir administered in combination with peginterferon and ribavirin largely resembles the known safety profile of PR standard of care therapy. The addition of boceprevir to peginterferon and ribavirin did not increase the frequency of deaths, life-threatening AEs, or study drug discontinuations due to AEs.
- Anemia was reported more frequently with boceprevir therapy, as were dose modifications for anemia, and the use of erythropoietin for the management of anemia. Study drug discontinuations for anemia were rare. The majority of patients who received erythropoietin responded well and were able to remain on therapy longer. Anemia was consistently associated with higher SVR rates.
- Neutropenia, and to a lesser extent thrombocytopenia, were reported more frequently with boceprevir therapy.
- There was no evidence to suggest that the rash reported with boceprevir differed in character or severity from that described in conjunction with ribavirin. There were no reports of Stevens-Johnson syndrome/toxic epidermal necrolysis.
- Dysgeusia (an altered sense of taste) was reported with boceprevir therapy, but was not severe or treatment limiting.
- The addition of boceprevir to peginterferon and ribavirin was generally well tolerated in patients with cirrhosis.

11.0 SAFETY MONITORING PLAN

A comprehensive safety monitoring plan has been developed for boceprevir. Components of this plan include pharmacovigilance activities, clear product information, patient and physician education, and expansion of existing patient resources.

Enhanced post-licensure pharmacovigilance activities will include the use of a targeted questionnaire to capture information on spontaneous reports of anemia. This questionnaire will ask for information about how this condition was managed and if there were clinical consequences. Other events which will be monitored closely include drug-drug interactions due to CYP3A4/5 inhibition, the development of resistance, and pregnancy exposures. The existing ribavirin pregnancy registry will be expanded to include exposures to boceprevir.

In order to optimize the safe use of boceprevir, several additional initiatives are planned. Professional educational materials will be developed to inform and instruct physicians and health care providers about the safe use of boceprevir (including a

response-guided therapy algorithm). A patient support program is also being developed.

A Medication Guide has been developed to provide safety information to patients and to encourage dialogue between the patient and health care provider. Specifically, the Medication Guide provides information about the potential for anemia and includes information on the signs and symptoms of anemia; the potential drug-drug interactions; the need to prevent pregnancy while on treatment; and warns against using boceprevir as monotherapy.

12.0 SUMMARY OF BENEFIT AND RISK OF BOCEPREVIR

Despite the success of pegylated interferons and ribavirin as standard of care treatment of chronic HCV infection, more effective regimens are needed. Clinical data indicate that boceprevir, a first generation HCV protease inhibitor, helps fulfill this medical need.

12.1 Benefits

The available efficacy data from clinical studies in treatment-naïve and previous treatment-failure patients support the conclusion that boceprevir has potent antiviral activity in the targeted patient population.

In the pivotal studies enrolling patients who were both treatment-naïve and patients who had previously failed peginterferon and ribavirin therapy, boceprevir increased SVR rates nearly 2-fold and 3-fold, respectively, compared to a standard 48-week course of peginterferon and ribavirin. Boceprevir provided consistent benefit across all subpopulations, including blacks and previous non-responders, demonstrating that boceprevir represents a substantial improvement over the current standard of care. Furthermore, very high SVR rates were achieved in patients who demonstrated early interferon responsive. Data from the long term follow-up study indicate the durability of SVR.

Use of a response-guided therapy algorithm allows for individualization of therapy and minimizes total treatment duration in patients with a response to therapy by treatment week 8. Response-guided therapy has the potential to provide significant benefit in terms of reducing drug-related adverse events associated with peginterferon, ribavirin, boceprevir, and erythropoietin.

Boceprevir offers a significant chance for all HCV-infected genotype 1 patients to achieve SVR. Although not assessed in the development program, the expected long term benefits of this increase in SVR rates include a lower incidence of end-stage liver disease, hepatocellular carcinoma, and need for liver transplantation. The predicted overall impact is a decrease in mortality related to chronic HCV infection.

12.2 Risks

Relative to the known profile of peginterferon and ribavirin, the addition of boceprevir was generally well tolerated. No specific safety issues have been identified that would preclude the use of boceprevir for the proposed indication. Addition of boceprevir to peginterferon and ribavirin results in a safety profile that largely reflects that of standard of care therapy alone. Nevertheless, important identified risks for boceprevir include anemia, CYP3A4/5 inhibition, and the emergence of resistance associated variants in patients who fail boceprevir therapy.

Anemia is a known adverse event in HCV-infected patients who are treated with PR standard of care regimens. Boceprevir added to PR causes an additional decrease of hemoglobin of about 1 g/dL. In clinical practice, the anemia observed with PR therapy is typically managed with ribavirin dose reduction and/or administration of erythropoietin, and these management strategies can also be used to manage the anemia seen when boceprevir is added to PR therapy. Neutropenia and thrombocytopenia were also reported with a higher incidence when boceprevir was added to PR compare to PR alone.

Boceprevir affects the plasma concentrations of drugs which are metabolized by CYP3A4/5, leading to increased exposures which could increase or prolong therapeutic effects and potential adverse effects. Boceprevir should not be coadministered with CYP34A substrates that have a narrow therapeutic index.

The emergence of HCV viral variants resistant to boceprevir occurs in some patients who fail boceprevir treatment. In general, resistance to direct acting antiviral agents in HCV infection is a new field. At this time, the relevance of RAVs and the implication for response to other protease inhibitors can not be fully addressed. The development of boceprevir RAVs may preclude successful response to other protease inhibitors which share the same RAVs. Data from the long-term follow-up study indicate that the quantity of resistant variants diminish over time.

12.3 Overall Benefit/Risk Assessment

Overall, the data presented indicate that the benefits of boceprevir outweigh the risks and support the proposed indication for boceprevir for the treatment of chronic hepatitis C genotype 1 infection in combination with peginterferon alpha and ribavirin in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy. The data also support the proposed dosage and administration in which treatment duration is individualized using a response-guided therapy algorithm.

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